Effect of Anaesthesia on Developing Brain

8

Pratishtha Yadav and Nishkarsh Gupta

8.1 Introduction

Brain is one of the most vital organs that influence an organism throughout the life. In the last two decades, animal studies have highlighted the neuroapoptotic and neurodegenerative effects of the anaesthetic drugs. This paved way for the numerous studies in humans, albeit retrospective. Most of them have clearly demonstrated an association between exposure to anaesthesia in infancy and development of behavioral problems later in life. So far, maximum evidence suggests that anesthetic drugs can influence the neurodevelopmental outcome of pediatric patients.

Recently, US Food and Drug Administration (FDA) has updated their statement that repeated or lengthy use of general anesthesia and sedative drugs during surgeries or procedures in children younger than 3 years or pregnant women during their 3rd trimester may affect the development of child's brain [1]. Thus, it is important to understand the role of anesthetic drugs in neurodevelopment so as to avoid long-term deleterious effects.

8.2 Brain Growth and Development

Differentiation of progenitor cells in the 3rd week of gestation marks the beginning of development of brain. It is an extensive process that progresses through multiple stages (Fig. 8.1). First is the formation of a neural tube. The ectodermal plate folds around a liquid-filled cavity creating the neural tube. This later gives rise to spinal cord enclosed in the spinal canal. Rest of the primary brain structure and ventricles arise from the vesicle-filled bulges at the anterior end of ectodermal plate. This whole process is the first step of brain development called **neurulation.** This is

The original version of this chapter has been revised by correcting an incorrect spelling of one of the author's names. A correction to this chapter can be found at https://doi.org/10.1007/978-981-19-5458-0_51

P. Yadav · N. Gupta (✉)
Onco-Anaesthesiology and Palliative Care, DR BRAIRCH, AIIMS, New Delhi, India

U. Saha (ed.), *Clinical Anesthesia for the Newborn and the Neonate*,
https://doi.org/10.1007/978-981-19-5458-0_8

Fig. 8.1 Stages in the Development of Brain

followed by the process of **neurogenesis,** which takes place in the early weeks of gestation, in the germinal matrix and subventricular zone. Epithelial progenitor cells lining the early ventricles differentiate into neurons and glial cells. At 12–20 weeks of gestation, neurons migrate to their final destination, the brain. At 20th weeks, the process synaptogenesis starts. The proliferation of neuronal synapses reaches its peak at 1–2 years of age. Synapse formation is the basis of learning throughout our life. Neuro-apoptosis or programmed cell death begins at 24th week of gestation and continues till 4th week after birth, i.e., in the neonatal period. Natural neuro-apoptosis takes place at a rate of 1% neurons per day, which reaches a peak in late gestation or early infancy. Final is the myelination of the axons which begins in the 2nd trimester and continues throughout childhood.

Neurotransmitters such as γ-aminobutyric acid (GABA), glutamate, and receptor system play a crucial role in neurodevelopment and are essential for maintenance of neuronal connections and in transmission of impulses. On the other hand, the absence of neuronal transmission and binding of GABA and glutamate stimulates neuro-apoptosis or cell death [2]. In the next section, we will discuss the impact of anaesthetic drugs on neuronal transmission and how they influence the complex process of neurodevelopment.

8.3 Suspected Pathways of Neurotoxicity

Anaesthetic drugs and sedatives are suspected to interfere with development of the brain by inducing neuro-apoptosis and disturbing the cerebral cytoarchitecture.

Role of GABA and NMDA receptors: Commonly used anaesthetic drugs and sedatives act via GABA receptor, or N-methyl-D-aspartate receptor (NMDA—a subtype of glutamate receptor). GABA-binding agents include volatile anaesthetic agents, propofol, benzodiazepines, barbiturates, etomidate, and chloral hydrate (Table 8.1). Nitrous oxide, and ketamine bind to NMDA receptors [3].

GABA receptors are inhibitory in nature, but due to an unknown mechanism, they act as excitatory during the developmental phase [4]. It is seen that refinement of the neuronal circuits takes place by activation of GABA receptors. Activation of the receptors induces cell migration, synaptogenesis, DNA synthesis, and cell proliferation. Antagonistic action of anaesthetic agents on these receptors can disturb this physiological neurodevelopment. Animal studies have confirmed the neurotoxic profile of NMDA antagonists and GABA agonists [5].

Synapse formation is an important component of brain development. Anaesthetic exposure in rodents leads to decrease (postnatal days 5–10) as well as increase (postnatal days 15–20) in the synapse density [6]. This brings forth the fact that exposure to clinically relevant doses of anaesthetics, whether short, prolonged, or multiple, can modify neuronal cytoarchitecture.

Table 8.1 Anesthetic drugs and their effect on various receptors

Agent	GABA	NMDA	Opioid receptor	Alpha2 adrenergic
Halogenated agents (sevoflurane, isoflurane, desflurane)	+			
Nitrous oxide		–		
Benzodiazepines	+			
Propofol	+			
Barbiturates	+			
Etomidate	+			
Chloral hydrate	+			
Ketamine		–		
Opioids			+	
Dexmedetomidine				+

GABA γ-Aminobutyric acid, *NMDA* N-methyl-D-aspartate; + Agonist; – Antagonist

Apart from neurogenesis, DNA-programmed neuronal death is equally important. During early developmental phase, excess of neurons and synapses are generated, which are reduced to less than 50% in adult life. Any interference with the normal apoptotic process can be detrimental to the neural architecture. Interference with the normal functioning of the GABA and NMDA receptors can lead to synaptic deprivation which in turn activates intrinsic neuro-apoptotic cascade.

Another mechanism is the anaesthesia-mediated mitochondrial disruption with release of caspase 9, the final executioner of cell death [2].

Role of calcium: calcium is for neuronal transmission. Endoplasmic reticulum (ER) is the primary regulator and source of calcium. Elevation of intracellular calcium is necessary for signalling, but excessive and prolonged exposure can be lethal. ER is considered an important initial target for anaesthetic agents. Exposure of anaesthetic agents in young animals is associated with prolonged elevation of intracellular calcium triggering neurotoxicity. Other suggested mechanisms include mitochondrial inhibition and energy depletion.

Neurotrophins: brain-derived neurotrophic factor (BDNF) is a type of neurotrophin. It plays a crucial role in neuronal survival and differentiation by activation of Trk receptors. It has been observed that if BDNF acts via p75NTR, it inhibits neurogenesis. Volatile anaesthetics and propofol increase the affinity of pro-BDNF toward p75NTR than Trk receptors, decreasing the neuronal survival [7]. Gross morphological changes can be easily detected by histological assessment, but sometimes even in the presence of normal looking neurons, abnormality may lie in the neuronal communications. Significant impairment in synaptic transmission in hippocampus of adolescent rats has been reported when exposed to anaesthesia on PD 7. Normal functioning of these circuits plays a crucial role in memory and learning later in life. Connections carrying inhibitory transmission are affected more.

Epigenetic Modification: Epigenetics is the study of heritable changes in the gene expression without changes in DNA. Recent reports have suggested that intrauterine exposure to anaesthetic drugs can induce cognitive impairment in 2nd

generation off springs [8]. The mechanism is still unknown, but there is a risk of intellectual disability and autism due to epigenetic changes in the progeny as well.

8.4 Human Studies vs Preclinical Studies

Attention was drawn toward the effect of anaesthesia exposure on neurodevelopment only after findings in the laboratory. Prior to this, anaesthesia-related toxicity was not considered. With growing evidence from preclinical studies, it has become even more important to determine if anaesthesia exposure can lead to clinically relevant neurodevelopmental side effects. The question is not straight forward. There are multiple domains associated with it, like time/duration of anaesthesia exposure, subpopulation affected, and type of neurodevelopmental function affected. However, direct reciprocation of preclinical data onto the human population may be imprecise.

Research has been conducted to study impact of anesthetic exposure in utero in rodent and non-human primate fetuses. Anesthetic drugs (isoflurane, propofol) administered for the duration of 4–5 h at the gestational age, equivalent to the 2nd and late 3rd trimester in humans, led to anaesthesia-induced neuro-apoptosis [9]. Another ovine study with isoflurane exposure in the mid-gestation failed to demonstrate any adverse effect with single exposure but, repeated exposures led to significant neuronal cell damage. However, these studies involved only anaesthesia and no surgery, which can confound the results. Another rodent study, with both anaesthesia and surgical exposure, has demonstrated conflicting results.

So far, majority of the studies have been done in the animal fetal and neonatal models, but they have several shortcomings. First, the interspecies differences in the brain development cannot be ignored. Second, most studies lack surgical stimulation. The negative impact of surgical stress, pain, tissue trauma on neurodevelopment is still unknown, but cannot be ignored. Third, the standard multiparameter monitoring done in humans is usually not practiced in majority of animal studies. This may be due to small size of neonatal animals and small circulating blood volumes precluding repeated blood gas analysis and glucose measurements. Fourth, most preclinical studies lack precision with regard to duration of exposure, specific age group, and specific functional defect. However, the consistent and reproducible adverse neurodegenerative and neurobehavioral effects seen in the animal models encourage scientists to explore the same on human fetus, infants, and young children exposed to anaesthetic agents.

8.5 Effect of Drugs in Utero and Maternal Exposure

8.5.1 Anaesthesia and Pregnant Mother

A large number of pregnant women require anaesthesia for obstetric and nonobstetric surgeries each year. Most commonly neuraxial anaesthesia is administered for caesarian surgeries. Majority of the surgeries take place at or near term, but

emergent surgeries can take place any time during the gestation. In case of an emergent surgeries or maternal contraindication for neuraxial anaesthesia, inhalation-based general anaesthesia is the preferred mode. Considering the duration of cesarian delivery, the anaesthesia exposure time is usually short. So far, the results are rather conflicting. A retrospective study in patients undergoing caesarian delivery found no differences between the two modes of anaesthesia (general anaesthesia and neuraxial anaesthesia) as well as vaginal delivery without any anaesthetic. However, a population-based study of neonates following cesarian delivery under general anaesthesia demonstrated higher incidence of autism as compared to neonates delivered under neuraxial anaesthesia or vaginal delivery without any anaesthetic [10].

8.5.2 Anaesthesia and Fetus

With advancement in fetal surgery, there is a surge in the incidence of in-utero surgeries. The commonly known indications are fetal surgeries for myelomeningocele, sacrococcygeal teratoma, and other congenital anomalies, also ex-utero intrapartum therapy (EXIT). These procedures demand general anaesthesia with adequate uterine relaxation, maternal and fetal analgesia, and appropriate surgical access. With inhalational agents, one is able to achieve adequate, precise, and predictable uterine relaxation, most suitable for in-utero surgeries. Other surgeries such as fetoscopy-guided selective laser photocoagulation for twin–twin transfusion syndrome (TTTS) and tracheal occlusion for congenital diaphragmatic hernia (CDH) can be performed with maternal local anaesthesia and sedation (fentanyl or remifentanil) along with fetal medications. With the growing concern associated with the negative impact of anaesthesia on fetal neurodevelopment, we face few important questions. First, utility or need of fetal procedure requiring anaesthesia exposure. Some of the surgeries such as myelomeningocele and TTTS have proven beneficial to the fetus, unlike others like tracheal occlusion for CDH, benefits of which are still under review. Second, significant number of paediatric patients with congenital cardiac anomalies suffers from neurological impairment independent of treatment.

Information regarding in-utero studies is very limited. Duration may vary from standard to lengthy surgeries depending upon the urgency and type of procedure. Information regarding pharmacokinetics and pharmacodynamics of anaesthetic drugs in fetus is also very limited. Moreover, there is always an ethical dilemma associated while conducting any such study specifically in humans. Like, randomization of patients to regional anaesthesia group may pose a challenge as general anaesthesia is usually considered appropriate as per maternal and fetal safety is concerned. Suitable alternative is prospective follow-up of children undergoing in-utero surgery with respect to neurological development. Plasticity or ability of the fetal brain to recover from neuronal/axonal injury during the early phase of brain development is still unclear. More research is urgently required in this field.

Neuraxial anaesthesia can be considered as the primary mode of anaesthesia whenever feasible. General anesthesia via inhalational agents can be kept as a reserve for emergent nonobstetric surgeries or procedures/patients with contraindication for neuraxial anaesthesia. Only sedation requiring fetal procedures can be performed with the help of intravenous opioids such as fentanyl, remifentanil as monotherapy or with neuraxial anaesthesia with local anesthetics such as lidocaine, and bupivacaine, instead of agents implicated by FDA (midazolam, propofol). Communication and allaying maternal anxiety is equally important. For uterine relaxation, specially of prolonged duration (>3 h), other tocolytic agents, such as intravenous nitroglycerine (NTG) or magnesium sulfate ($MgSO_4$) or Atosiban, may be considered. There are limitations with these drugs, e.g., titrating the dose of NTG, while Atosiban and $MgSO_4$ have limited efficacy, making them unsuitable as sole tocolytics, but can be used as adjuncts to enhance uterine relaxation and reduce the requirement of inhalational agents. Another alternative is opioid supplementation with sparing effect on inhalational agents at the critical period when maximum relaxation is required during fetal manipulation.

Most preclinical studies suggest detrimental effect of high concentration and prolonged exposure of inhalational agents (Table 8.2). However, the exact concentration and duration have not been elucidated. FDA warning also lacks recommendations for exact dose or concentration of the anaesthetic agents to avoid.

Table 8.2 Type of surgery and choice of anesthesia technique

Type of surgery	Anaesthetic technique	Suggested modifications
Obstetric	Neuraxial block—LA ± opioids	None
Nonobstetric, Nonemergent	Neuraxial block—LA ± opioids	None
	Inhalation-based GA	<3 h duration—no change >3 h durations—consider deferring until postpartum
Nonobstetric (emergent)	Inhalation-based GA	Limit times: (a) Between induction and start of surgery (b) Between end of surgery and end of anesthesia.
Fetal procedures	LA/neuraxial anaesthesia	None
	IV sedative-hypnotic—propofol/ Midazolam	<3 h duration—no change >3 h duration—discuss risk/benefit Consider IV opioids (fentanyl or remifentanil) or dexmedetomidine
	GA with inhalational agents	<3 h duration—no change >3 h duration—discuss risk/benefit
	GA with increased concentration of inhalational agents for uterine relaxation	Consider supplementing with $MgSO_4$, Atosiban or NTG for tocolysis

LA Local anesthesia, *GA* General anaesthesia

8.6 Factors Affecting Neurotoxicity

8.6.1 Drug Type

Effect of inhalational agents on neurodegeneration and behavioral deficits is now accepted.

Isoflurane activates inositol 1,4,5-triphosphate receptors and induces excessive release of calcium from ER, modulating mitochondrial Bcl-xl protein ultimately initiating neural cell apoptosis. Similar mechanism is also reported with propofol, desflurane, and sevoflurane leading to uncontrolled release of pro-apoptotic factors [11].

Histopathological examination of brain of PD6 rhesus monkey after 5 h exposure to surgical plane of isoflurane anaesthesia revealed significant neuro-apoptotic changes as compared to age-matched controls. It was interesting to note that apoptosis was not confined to neurons, but large proportion of glial cells were also affected. Oligodendroglia plays a crucial role in the myelination of the neuronal axons. The study was repeated at the timepoint corresponding to the early stage of myelogenesis (gestational age of 120 days in monkeys). On examination, widespread neuronal apoptosis was noted in several cerebral cortical regions along with dispersed apoptosis of oligodendrocytes in the white matter region. Similar observations were made with propofol. Very recent reports have reported similar damage even with shorter exposure times (<3 h) also.

Prolonged exposure of sevoflurane (2.5% for 9 h) in nonhuman primates is associated with modulation of gene expression and impairment of lipid metabolism. Ketamine, widely used in children, is also associated with developmental abnormalities. A study reported that early developmental stages (122 days of gestation and 5 PD) are more susceptible to ketamine-induced neuronal death as compared to late that is 35 PD in resus monkeys. Long-term cognitive impairments such as learning, psychomotor skills, concept formation, and motivation were also affected, in the coming years. However, in this study, ketamine was administered for 24 h, which is quite unusual in clinical scenario. Later, shorter exposure times (5 h),, also demonstrated significant neuro-apoptosis.

8.6.2 Exposure Time

When it comes to exposure time, whether short or long, the results are unclear, both in animal and human studies. The positive vs negative studies ranged between 40 and 50% for exposure time of less than 1 h. However, the same ratio increases to 80% when exposure time is increased to more than 3 h. Most recent randomized control trials have also failed to demonstrate any effect with single and brief exposure in early infancy [12]. PANDA study also failed to detect any significant difference in IQ in between siblings with and without anaesthesia exposure (median exposure time of 80 min). On the contrary, in a cohort study from Western Australia, extensive neurobehavioral testing was done in children who underwent anaesthesia

and surgery prior to the age of 3 years. They reported that with exposure as low as 15 min was associated with defective language and abstract reasoning later in life as compared to unexposed children.

8.6.3 Number of Exposures

Multiple anaesthesia exposures lead to cumulative effect and may be cause functional and structural alterations in the brain. On the other hand, single exposure is not completely devoid of any adverse neurodevelopmental effects. Wilder et al. studied the impact of single vs multiple exposures in more than 500 children and found that those with more than one exposure developed learning disabilities later in life [13].

8.7 Age of Exposure

8.7.1 Window of Vulnerability

Exposure to anaesthetic agents leads to neuronal cell death in the developing brain, which ultimately leads to neurodevelopmental defects as the child grows [14]. It is postulated that there is a specific time-period, the **window of vulnerability,** when the anaesthetic exposure may be particularly deleterious. In rodents, peak sensitivity is expected between postnatal days 7 and 10, followed by reduced sensitivity after day 10, and no effect beyond 60 days. However, this may be different in humans considering the developmental differences between the two species. As per current scientific evidence suspected period of vulnerability is expected to be during synaptogenesis, which ranges from birth to 2–4 years of age. However, high level of heterogenicity in the current evidence adds uncertainty to the acceptance of this hypothesis especially as to the period of vulnerability.

A recent large-scale observational cohort study concluded that children undergoing minor surgery and anaesthesia exposure before the age of 5 years are at a statistically significant increased risk of mental disorders, developmental delays, and attention deficit hyperactivity disorders (ADHD). The most significant observation was that the risk was found to be uniform regardless of age of exposure in the 5 year age period [15].

Based on the results of animal studies, it can be understood that the immature stages of human brain development in the antenatal period are most vulnerable to anaesthetic agents. On the other side, studies beyond the prenatal period also have failed to ensure safety of anaesthetic agents. Thus, there is still no specific age beyond which anaesthetic agents can be considered safe.

With all these considerations and limitations, FDA warns against use of anesthetics in children under the age of 3 years.

However, as a clinician and anesthetist, one must balance delaying the anaesthesia exposure with the unintended harmful consequences of delaying the surgery (Fig. 8.2) [1].

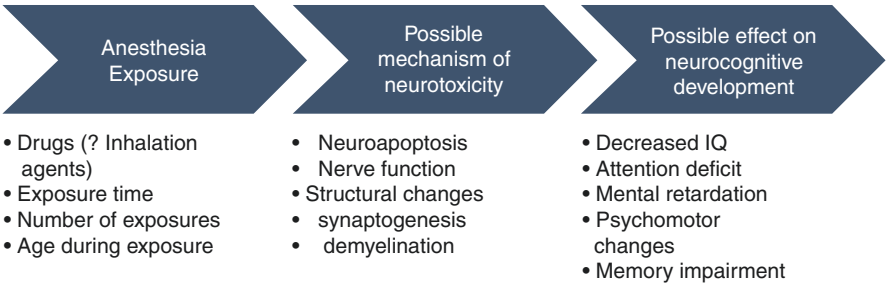

Fig. 8.2 Anesthetic Agent Induced Neurotoxicity

8.8 Clinical Implications of Potential Anesthesia-Related Neurotoxicity

The greatest dilemma for the anaesthesiologist will arise at the time of informed consent taking from the parents and ensuring safety of their child. All anesthetic agents, including nitrous oxide, have been implicated in causing cerebral neurotoxicity, affecting brain development and growth, with potential long-term deficits. Question arises then should we give anesthesia to these babies?? Unlike animal studies, whose data are being extrapolated to humans, and where anaesthetics are given without surgical indications, in human babies, anesthesia is provided for a surgical procedure. Because of the surgical condition, there may already be effects on various organ systems (pulmonary and gas exchange, hepatic renal and cardiac effects, metabolic, and acid base changes neurological changes (lethargy, somnolence, seizures, etc.).

On top of that blaming anesthesia for potential adverse neurotoxicity and long-term effects, seems unfair, as is depriving a surgical neonate of anesthesia.

Still, considering the scientific data in this field, however, limited and mostly from animals, it is imperative that proper precautions are taken while dealing with procedures requiring anesthetic exposure to prevent add-on effects on the growing brain of the fetus, or newborn, or neonate, depending on the situation.

Hence, safest course to be adopted by the concerned clinicians includes:

1. Undertake only that surgery which is urgent, life or organ saving
2. Use of adjuvant techniques (regional, local, or neuraxial anesthesia) so as to reduce the requirement of general anesthetic drugs
3. Precautions during regional anesthesia to use diluted concentrations of the LA drugs and never exceed toxic dose
4. Use the lowest possible anesthetic doses for shortest possible times, minimizing any potential brain effects
5. Use of safer drugs, e.g., fentanyl, remifentanil instead of morphine and pethidine, and avoiding propofol, and inhalational agents, as far as possible
6. Limited duration of surgery and hence anesthesia—total duration of anesthesia should not exceed 3 h

7. Minimising the duration of anaesthetic exposure for fetal, obstetric and nonobstetric procedures, by reducing the time interval between anaesthesia induction and start of surgery
8. Using of drugs and in doses, so that it does not prolong recovery time after anesthesia (i.e., end of surgery to extubation or recovery), for example, following a short surgery of 30 min should not be accompanied by prolonged or delayed recovery from anesthesia
9. Intrauterine surgeries and EXIT procedures require good uterine relaxation, so that surgical manipulations do not stimulate uterine contractions, and fetal morbidity and mortality. This is usually achieved by high doses of volatile anesthetic agents. Hence, to reduce their requirement, adjuvant tocolytic agents should be used instead, e.g., Corticosteroids, $MgSO_4$, Terbutaline, and Ritodrine
10. Use of alternative analgesic drugs and techniques Remifentanyl, Fentanyl, local infiltration, and reginal blocks including caudal block
11. BP, blood flow to brain and levels of CO_2 and O_2, may also play a role in protecting the brain. Using drugs and techniques that will create minimal hemodynamic and gas exchange disturbances and careful intraoperative monitoring

8.9 Future Direction

1. There is an urgent need to conduct research in the future keeping in mind the lacunae in the current evidence, with a multifaceted approach involving preclinical scientists, neuropsychologists, neonatologists, developmental paediatricians, neurologists, toxicologists, epidemiologists, and the anaesthesia community
2. Basic and translational high-quality preclinical studies to evaluate mechanism of toxicity with proper documentation of the anaesthesia technique and duration of exposure
3. Cohort studies with large sample size to detect small outcome differences in the neurodevelopmental domains, sufficient enough to establish clinical risk modifiers
4. Planning of high-quality clinical trials with adequate power in specific age groups focusing on specific interventions to achieve clinically relevant results

8.10 Conclusion

Exposure to general anaesthesia in fetus and early childhood is associated with neurodevelopmental anomalies later in life. Several preclinical studies have pointed toward possible mechanisms for neurotoxicity, but their implications on humans are still unclear. Genetic, physiological, and developmental interspecies differences limit the translation of animal and preclinical results to humans. Recent FDA warning cautioning against frequent prolonged anesthesia in small children **"repeated or lengthy use of general anesthesia and sedation drugs during surgeries or**

procedures in children younger than 3 years or pregnant women during their third trimester may affect the development of children's brains" must be paid heed to.

References

1. FDA Drug Safety Communication: FDA approves label changes for use of general anesthetic and sedation drugs in young children. Nov, 2017; https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-approves-label-changes-use-general-anesthetic-and-sedation-drugs
2. Sanders RD, Hassell J, Davidson AJ, Robertson NJ, Ma D. Impact of anaesthetics and surgery on neurodevelopment: an update. Br J Anaesth. 2013;110(suppl 1):i53–72.
3. Istaphanous GK, Ward CG, Loepke AW. The impact of the perioperative period on neurocognitive development, with a focus on pharmacological concerns. Best Pract Res Clin Anaesthesiol. 2010;24:433–49.
4. Tashiro A, Sandler VM, Toni N, et al. NMDA receptor mediated, cell-specific integration of new neurons in adult dentate gyrus. Nature. 2006;442(7105):929–33.
5. Gentry KR, Steele LM, Sedensky MM, et al. Early developmental exposure to volatile anesthetics causes behavioral defects in Caenorhabditis elegans. Anesth Analg. 2013;116(1):185–9.
6. Head BP, Patel HH, Niesman IR, et al. Inhibition of p75 neurotrophin receptor attenuates isoflurane mediated neuronal apoptosis in the neonatal central nervous system. Anesthesiology. 2009;110(4):813–25.
7. Suehara T, Morishita J, Ueki M, et al. Effects of sevoflurane exposure during late pregnancy on brain development of offspring mice. Paediatr Anaesth. 2016;26(1):52–9.
8. Chalon J, Tang CK, Ramanathan S, et al. Exposure to halothane and enflurane affects learning function of murine progeny. Anesth Analg. 1981;60(11):794–7.
9. Creeley C, Dikranian K, Dissen G, Martin L, et al. Propofol induced apoptosis of neurones and oligodendrocytes in fetal and neonatal rhesus macaque brain. Br J Anaesth. 2013;110(Suppl 1):i29–38. https://doi.org/10.1093/bja/aet173.
10. Chien LN, Lin HC, Shao YH, et al. Risk of autism associated with general anesthesia during cesarean delivery: a population-based birth-cohort analysis. J Autism Dev Disord. 2015;45(4):932–42. https://doi.org/10.1007/s10803-014-2247-y.
11. Inan S, Wei H. The cytoprotective effects of dantrolene: a ryanodine receptor antagonist. Anesth Analg. 2010;111:1400–10.
12. Davidson AJ, Disma N, de Graaff JC, Withington DE, et al. Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial. Lancet. 2016;387:239–50.
13. Wilder RT, Flick RP, Sprung J, Katusic SK, et al. Early exposure to anesthesia and learning disabilities in a population based birth cohort. Anesthesiology. 2009;110:796–804.
14. Jevtovic-Todorovic V, Hartman RE, Izumi Y, et al. Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. J Neurosci. 2003;23:876–82.
15. Ing C, Sun M, Olfson M, DiMaggio CJ, et al. Age at exposure to surgery and anesthesia in children and association with mental disorder diagnosis. Anesth Analg. 2017;125(6):1988–98. https://doi.org/10.1213/ANE.0000000000002423.