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THE EFFECT OF GENERAL ANESTHETICS ON COGNITIVE FUNCTIONS IN CHILDREN

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ABSTRACT. ***Introduction.*** Recent work and accumulated knowledge over several decades have shown that general anesthetics are potentially toxic to a child's developing brain. In many animal studies, it has been found that after exposure to anesthesia, neuroinflammation, apoptosis of neurons occurs at certain stages of brain development, and persistent cognitive impairment subsequently forms. A number of cohort studies are alarming in assessing the intellectual development of children who underwent general anesthesia at the age of 3 years. Several studies have found a link between the use of anesthesia in early childhood and the subsequent development of cognitive impairment, the appearance of learning problems. ***The purpose of the work*** is to present the results of a systematic review of publications on the problem of the effect of general anesthesia on the cognitive functions of a child. The search for publications was carried out by analyzing PubMed electronic bibliographic databases. ***Result.*** In our study the analysis of preclinical studies, as well as the largest retrospective and prospective clinical studies, is carried out; problems in identifying biomarkers associated with the neurotoxicity of general anesthetics are identified; the role of surgical intervention and changes in homeostasis in the formation of postoperative cognitive dysfunction is considered. ***Conclusion.*** At the moment, there is no convincing evidence that a single and short exposure (less than 1 hour) to general anesthesia in early childhood has a causal relationship with a negative effect on the neurocognitive functions of the child. Repeated exposure to anesthetics can lead to deterioration of some of the child's skills. There is a need to conduct new studies related to the prolonged effect of general anesthesia (more than 1 hour) on the nervous system of children, to identify the dependence of the severity of neurotoxicity on the duration of anesthesia and the choice of anesthetic. There is a need to identify suitable biomarkers associated with the neurotoxicity of general anesthetics. It is necessary to study the role of surgical intervention, the type of operation, and temporary changes in systemic homeostasis in the formation of postoperative cognitive dysfunction in children.

KEYWORDS: *general anesthesia, neurotoxicity, anesthetics, biomarkers, postoperative cognitive dysfunction, childhood*

ВЛИЯНИЕ ОБЩИХ АНЕСТЕТИКОВ НА КОГНИТИВНЫЕ ФУНКЦИИ У ДЕТЕЙ

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РЕЗЮМЕ. ***Введение.*** Последние работы и накопленные за несколько десятилетий знания показали, что общие анестетики потенциально токсичны для развивающегося мозга ребенка. Во многих исследованиях, проведенных на животных, было установлено, что после воздействия анестезии на определенных этапах развития головного мозга возникает нейровоспаление, апоптоз нейронов и впоследствии формируются стойкие когнитивные нарушения. Вызывает настороженность ряд когортных исследований при оценке интеллектуального развития детей, перенесших общую анестезию в возрасте до трех лет. В нескольких работах обнаружена связь между применением наркоза в раннем детском возрасте и последующим развитием нарушений когнитивных функций, а также появлением проблем в обучении. ***Цель работы*** — представить результаты систематического обзора публикаций о проблеме влияния общей анестезии на когнитивные функции ребенка. Поиск публикаций был осуществлен путем анализа электронных библиографических баз данных PubMed. ***Результаты.*** Произведен разбор доклинических исследований, а также наиболее крупных ретроспективных и проспективных клинических работ. Обозначены проблемы в выявлении биомаркеров, связанных с нейротоксичностью общих анестетиков. Рассмотрен вопрос роли хирургического вмешательства и изменения гомеостаза в формировании послеоперационной когнитивной дисфункции. ***Заключение.*** На данный момент нет убедительных данных о том, что однократное и короткое воздействия (менее 1 часа) общей анестезии в раннем детском возрасте имеет причинно-следственную связь с негативным влиянием на нейрокогнитивные функции ребенка. Многократное воздействие анестетиков может привести к ухудшению некоторых навыков ребенка. Имеется необходимость в проведении новых исследований, связанных с продолжительным воздействием общей анестезии (более одного часа) на нервную систему детей и зависимости выраженности нейротоксичности от длительности анестезии и выбора анестетика. Существует необходимость в определении подходящих биомаркеров, связанных с нейротоксичностью общих анестетиков. Требуется проведение новых работ, изучающих роль хирургического вмешательства, вида операции, временного изменения системного гомеостаза в формировании послеоперационной когнитивной дисфункции у детей.

КЛЮЧЕВЫЕ СЛОВА: *общая анестезия, нейротоксичность, анестетики, биомаркеры, послеоперационная когнитивная дисфункция, детский возраст*

INTRODUCTION

The anesthesiologist informs children and parents about the possible risks associated with the use of anesthesia. Some complications, such as damage to the lips and teeth, anaphylaxis, regurgitation of gastric contents into the airways, sore throat, nausea and vomiting, may occur immediately. But there is a risk that is much more difficult to assess — the effect of the anesthetic on the developing brain of the child. Parents are increasingly interested in the neurocognitive functions of their children after general anesthesia, although many anesthesiologists still rarely assess the possible risks of developing cognitive dysfunction during the preoperative check-up. The relevance of the topic is due to the prevalence of surgical interventions and diagnostic studies requiring anesthesia during periods of development of the child's nervous system. Initially, the results obtained during pre-clinical animal research showed that the basis for changes in cognitive functions after anesthesia is neuronal apoptosis (programmed death) during the formation of synaptic connections [1]. The observed neurodegeneration caused alarm, and many animal research, as well as clinical trials, began to focus on this issue.

The article provides a systematic review of publications on the problem of the effect of general anesthesia on cognitive functions in children. The initial data of preclinical research, early retrospective clinical analyses on this topic, and the results of recent cohort studies are discussed. Based on this, the problems and prospects for new studies are identified. The review includes articles published from 1981 to 2023. The search for publications was carried out by analyzing PubMed electronic bibliographic databases in the spring of 2024. The research request included the following words and phrases: post-operative cognitive dysfunction, anesthesia. Based on the search results, 960 records were identified in the databases, of which 783 articles were recognized as potentially relevant. When assessing the relevance of the content of these articles, a set of 45 publications was formed, presented below. The analysis was carried out on articles published in English and Russian.

ANIMAL RESEARCH

The study of the effect of anesthetics on the central nervous system is an important aspect of the safety of using these agents in clinical practice. Studies of the toxic effect of general anesthetics on the developing brain have been conducted for several decades and continue to be actively carried out until now. As early as 1981, an article entitled “Exposure to halothane and enflurane affects learning function of murine progeny” was published in the journal Anesthesia & Analgesia [2]. This experiment showed that mice exposed to halothane or enflurane in utero were worse in maze performance than control group, which was not exposed to anesthetics. Moreover, in some cases, learning disorders were also detected in the next generation of mice exposed to halothane.

Important study was published in 1999 in the journal Science, “Blockade of NMDA receptors and apoptotic neurodegeneration in the developing brain” [1]. This work established a link between early exposure to NMDA receptor antagonists and the development of neuroapoptosis in rat pups. In the following years, the number of studies and publications only grew, and it became increasingly clear that the effects of anesthetics on the central nervous system of animals are indeed toxic. Exposure to anesthetics can cause both neuroapoptosis and significant behavioral disturbances in animal models, such as mice, rats, guinea pigs, and non-human primates [3–5].

The fact that in non-human primates adverse effects were detected a comprehensive manner at the biochemical, morphological, histopathological and behavioral levels was of particular concern [6]. The results in the presented studies raised a new question: can the data obtained in animal research be extrapolated to humans? Given the growing amount of information obtained from preclinical research, the United States Food and Drug Administration (FDA) has made recommendations in 2007 that *elective procedures involving general anesthesia in children under 3 years of age should be delayed whenever possible*. The committee also concluded that *additional studies are needed to understand the significance of data on the effects of anesthetics on animals for children who*

will be exposed to general anesthesia. Since then, many animal studies and clinical trials have focused on this issue [7].

At the same time, the FDA statement provided was the impetus for new studies that needed to assess neurological disorders in children exposed to general anesthesia in the long term. With the support of the FDA and IARS (International Association for Reconciliation Studies, International Anesthesia Research Society), the SmartTots program (https://smarttots.org/) is being created. Its aim is to assess the effect of anesthetics on children's development, as well as to assist and support scientists working in this field. It was after the FDA statement of 2007 that several large and important studies were conducted on this topic.

RISING ALARM

Several studies were published at once in 2009, addressing the topic of postoperative cognitive dysfunction in children. One of them is an observational study by C. DiMaggio et al. [8]. A cohort of 383 children who had undergone inguinal hernia repair within the first three years of life was selected. They were compared with 5,050 subjects of similar age who had not had surgery performed for up to three years. It was found that behavioral disorders and developmental delays were detected more than twice as often in children who had undergone surgery. Then the same authors conducted another large study to determine the influence of environmental factors [9]. A cohort of 10,450 siblings was formed, from which a group of 304 children exposed to general anesthesia before the age of three years was isolated. A comparison was also made with 10,146 siblings who did not undergo surgery and were not exposed to general anesthetics before the age of three years. The study found that behavioral deviations and neurodevelopmental disorders were 60% more common in children who had surgery. Moreover, the estimated odds ratio for developmental or behavioral disorders increased with multiple surgeries. It was 1.1 (95% CI 0.8–1.4) for one surgery, 2.9 (94% CI 2.5–3.1) for two surgeries, and 4.0 (95% CI 3.5–4.5) for three or more surgeries.

In 2009, the results of a population-based retrospective study by R.T. Wilder et al. were also published, which examined the effects of anesthetics on children under four years of age. Scientists selected a group of 5,357 children, of which 593 children were exposed to general anesthesia. The study found that subjects who had undergone general anesthesia once before the age of four showed results comparable to the control group. However, the results in reading, writing, and mathematics in children had been given general anesthesia several times were noticeably worse, and learning difficulties were detected more often [10].

One of the stages of research was the comparison of twins. M. Bartels et al. published an article in which 1143 pairs of identical twins from the Netherlands Twin Register were analyzed [11]. Separately, pairs of twins were identified in which one or both of the siblings had undergone general anesthesia before the age of three. It is worth noting that the authors did not take into account the duration of general anesthesia and the nature of the surgical intervention. The results showed that at age 12, the twins exposed to anesthesia before age 3 had significantly lower academic performance and more cognitive problems than the twins who were not exposed to anesthesia. It is interesting that study presented has an important nuance: the same poor academic performance was demonstrated by the twins who did not undergo anesthesia from the observed pairs, not differing directly from their exposed siblings. This information excludes a causal relationship between the effects of anesthetic on the child's nervous system.

It should also be mentioned that in addition to the general study, the above-mentioned work by C. DiMaggio et al. [9] also assessed 138 pairs of twins, in which one child had undergone surgery and the other had not. In this part of the analysis, it was found that, just as in the article by M. Bartels et al., when assessing pairs of discordant twins, the risk of developing neurological disorders was not significantly associated with the effects of general anesthesia. Such discrepancies in the results raised even more questions, and it became clear that a more in-depth analysis of the existing problem was needed. There was a need to conduct larger-scale studies, including randomized

clinical trials [12]. Such studies included **GAS**, **MASK**, and **PANDA**, which will be discussed in more detail below.

GENERAL ANAESTHESIA OR AWAKE-REGIONAL ANAESTHESIA IN INFANCY (GAS)

The aim of the first multicenter randomized clinical trial was to identify the negative effects of a general anesthetic (sevoflurane) on the development of the nervous system of a child who underwent anesthesia in infancy. The study included 722 children from 7 countries at a postconceptional age of up to 60 weeks, born no earlier than 26 weeks' gestational age. All observed patients underwent inguinal hernia repair. The children were divided into two equal groups. In the first group, regional anesthesia was performed subjects in a waking state using bupivacaine or levobupivacaine. In the second group, sevoflurane was used for induction and maintenance of anesthesia. No additional opioid or nitrous oxide administration was permitted, but regional blockades with bupivacaine were allowed to provide postoperative analgesia. It is noteworthy that the mean duration of anesthesia in the general anesthesia group was 54 minutes. Follow-up neurodevelopmental assessments were performed at age 2 years (adjusted for prematurity) and for 4 months after age 5. In total, the study was completed for 205 subjects using awake-regional anesthesia and 242 using general anesthesia.

Based on the results of tests on the mental and neurocognitive development of children at the age of two and five years, no convincing differences in the intellectual development of the two groups were found. The results of the presented work allowed the authors to conclude that the effect of general anesthetic on a child in early infancy will not cause significant neurocognitive or behavioral disorders at the age of two and five years [13, 14].

MAYO ANESTHESIA SAFETY IN KIDS (MASK)

In the observational study under review, the authors aimed to evaluate the effect of general anesthetics on the nervous system of children who had undergone anesthesia several times before the age of three. The researchers selected a group of children born from January 1, 1994 to December 31, 2007. During the medical record review, the subjects were divided into three groups: 411 children who had not undergone anesthesia, 380 children who had undergone anesthesia once, and 206 children who had undergone anesthesia multiple times. Each group was subdivided into two age categories: from 8 to 12 years (preadolescence) and from 15 to 19 years (adolescence). It is noteworthy that such distribution was aimed not only at separating by age characteristics, but also due to the wider introduction of sevoflurane into anesthetic practice for the preadolescent group. Mean duration of general anesthesia was 45 and 187 minutes for patients who underwent general anesthesia once and multiple times, respectively. At the same time, 2/3 of the subjects who underwent multiple exposures were under anesthesia for more than two hours. According to the study, the most frequently used anesthetics were sevoflurane and nitrous oxide, and the most common types of surgical interventions were ENT and cardiovascular surgeries. Each child was assessed for intellectual development using the WASI (Wechsler Abbreviated Scale of Intelligence), then attention, reaction, visual-motor memory, etc. were analyzed using various tests. In addition, the parents of the children participating in the study compiled reports on the behavior, learning, and development of their child.

The results showed that subjects who had been repeatedly exposed to general anesthesia performed only slightly worse on the intelligence test than the group who had been exposed once and the children who had not been anesthetized at all. The available data allowed the authors to conclude that exposure to general anesthetics before the age of three is not associated with reduced intelligence in preadolescence and adolescence. Regarding the results of the child's skills, it is worth noting that only children exposed to repeated general anesthetics showed a decline in information processing speed and fine motor skills. Along with this, other skills among the groups, such as reaction, attention, verbal expression of thoughts, etc., were at a comparable level. It is also noted that parents of those children who had been repeatedly anesthetized more often reported

problems related to their children's behavior and reading [15].

PEDIATRIC ANESTHESIA NEURODEVELOPMENT ASSESSMENT (PANDA)

The PANDA project is a large multicenter study that aims to evaluate the development of the nervous system in children who underwent a single exposure to general anaesthesia for inguinal hernia repair before the age of three years. Two groups were examined: the children who had undergone anesthesia, and subjects' brothers and sisters who had not been exposed to anesthesia. Siblings had to be close in age with a difference of no more than three years. Children aged 8 to 15 years were assessed for cognitive function, as well as intelligence and behavior. A total of 105 pairs of siblings were analyzed in the study. All the patients who underwent anesthesia received inhalational anesthetics (43 sevoflurane, 5 isoflurane, 57 sevoflurane and isoflurane). Both inhalational and intravenous anesthetics (propofol, thiopental, ketamine and midazolam) were given to 28 patients. Additional opioid analgesia was administered to 75 subjects and 39 children received additional spinal anesthesia. Mean duration of general anesthesia was 84 minutes. The study found no significant differences in intelligence, memory, attention, behavior, or information processing speed among children who underwent general anesthesia before age three compared with their siblings who were not undergoing general anesthesia [16].

The results of the above-mentioned **MASK**, **GAS** and **PANDA** studies in many review articles are often considered together and cause heated discussions [17–20]. Subsequently, these works became the foundation for new studies on the effect of anesthesia on the nervous system of the child.

UNRESOLVED ISSUES AND NEW RESEARCH

The above studies were unable to fully resolve the issues raised by the FDA in 2007, which focused on the risks of general anesthesia in children. However, analyzing the results obtained in these studies, we can form a number of preliminary conclusions:

- probably, short-term single exposure to general anesthesia does not affect the neurocognitive functions of children in subsequent development;
- it is worth assuming that repeated exposure to general anesthetics has harmful effects on a number of children's skills, which causes reasonable alertness;
- there remains uncertainty associated with the long-term effect of general anesthesia (more than 1 hour) on the nervous system of children and dependence of the severity of neurotoxicity on the duration of anesthesia.

Despite many unanswered questions, in 2016 the FDA issued a new, tougher statement: "*Repeated or lengthy use of general anesthetics and sedation drugs during surgeries or procedures in children younger than 3 years or in pregnant women during their third trimester may affect the development of children's brains. Healthcare professionals should balance the benefits of anesthesia in young children and pregnant women against the potential risks, especially for procedures that may last longer than 3 hours or if multiple procedures are required in children under 3 years*" [21]. This notice caused a lot of discussion and debate among anesthesiologists [22–24]. The European Society of Anaesthesiology and Intensive Care even issued a response that they do not share the opinion of the FDA specialists. This was argued by the fact that at the moment there is no convincing data, confirmed by human studies, that would indicate any effect of prolonged or continuous anesthesia on neurocognitive abilities and development of children [25].

Debate continues to this day, but one thing remains clear: there are still insufficient studies to draw clear final conclusions [26–28]. Due to the difficulty of conducting randomized clinical trials of the neurotoxic effect of anesthetics and their impact on children's cognitive skills, only one large project, GAS, has been implemented. According to the analysis of published articles, since 2018, due to the shifting focus towards problems associated with the COVID-19 pandemic, interest in research on the neurotoxic effect of anesthetics has somewhat decreased [29]. However, scientific interest in the problem is gradually reviving, and a number of large clinical trials are currently underway. The study of Professor P. Szmuk et al. on the

T-REX trial stands out. A multicenter randomized clinical trial is being conducted, which compares infants who have been administered standard dose of sevoflurane with children who underwent combined anesthesia with low doses of sevoflurane, dexmedetomidine and remifentanil [30]. Duration of anesthesia considered in the study is 2 hours and more. A total of 440 newborns requiring surgery are randomly assigned to receive different types of anesthesia: standard doses of sevoflurane or combined anesthesia. The results of this research should clarify the impact of prolonged general anesthesia on the developing child's brain.

BIOMARKERS AND NEUROIMAGING

The study of neurotoxicity of general anesthetics is complicated by the difficulty of assessing cognitive status in young children. Most studies evaluate children's cognitive functions primary school or school age. Given the assumption that young patients under three years are most susceptible to the effects of anesthetics [21], there is a long delay between exposure to general anesthesia and assessment of its effects [31]. There is a need for long-term observation of children who have undergone anesthesia at an early age, and the likelihood of distortion of results due to environmental and other factors increases. Identification of suitable biomarkers associated with general anesthetic neurotoxicity may be extremely valuable for clinical trials. Biomarker detection could help assess interim outcomes and understand the mechanism of central nervous system injury. And if biomarker values can be linked to long-term outcomes, it may be possible to detect injury at an earlier stage, thereby reducing the time between anesthetic exposure and assessment of the effect. This, in turn, would reduce the need for long-term follow-up in clinical trials.

One of the biomarkers proposed for consideration by a number of authors is the level of **S100β** protein in serum or cerebrospinal fluid. Animal research has shown that S100β is effective in detecting acute neurological injury to the developing brain caused by general anesthesia [32–34]. An analysis of several studies has revealed a correlation between postoperative cognitive dysfunction and elevated S100β levels in adult patients [35]. However, studies conducted in children have had mixed results [36–38], and the assessment of the relationship between changes in S100β levels and postoperative cognitive dysfunction in children requires further study. In addition, obtaining cerebrospinal fluid from conscious children also causes certain difficulties, which complicates the use of cerebrospinal fluid biomarkers in clinical trials.

In connection with these facts, neuroimaging has become another alternative assessment of the neurotoxicity of anesthetics [39]. In 2015, a study was published in which magnetic resonance imaging (MRI) data showed a decrease in gray matter volume of in the brain of children who underwent anesthesia before the age of four [40]. Also, a recent study assessed the results of the MRI and neuropsychological indicators in 102 children aged 9 to 10 years, 24 of whom were exposed to general anesthesia in infancy. It turned out that subjects who were exposed to anesthesia had a decrease in gray matter volume of the right inferior frontal gyrus, as well as reduction in the ability to control their emotions [41]. In addition to measuring the volume of gray matter and other structures, MRI in children can be used to assess the interaction between different areas of the central nervous system (CNS) both during brain activation during certain cognitive tasks and tests and at rest without performing any tasks [42, 43]. It should be emphasized that there are currently no data that have clearly established the relationship between changes in the CNS according to MRI results and the presence of postoperative cognitive dysfunction in children, and future studies should be aimed at assessing structural disorders in combination with neuropsychological analysis. It should be noted that, although this method is promising, it has an obvious disadvantage — the difficulty of use in young children who require sedation for MRI.

IMPACT OF SURGICAL INTERVENTION AND OTHER FACTORS

Many studies have focused on the effects of general anesthetic on children's cognitive function. However, there is still little specific information on the role of surgery and type of surgical procedure on postoperative cognitive dysfunction in children. There is a lack of understanding of how a particular type of sur-

gery, combined with different types of general anesthesia, may affect a child's developing brain. For example, a study on seven-day-old rats found that prolonged anesthesia after exposure to nociceptive stimuli resulted in significantly greater apoptosis in the central nervous system compared to the situation when only general anesthesia was used [44]. An isolated study of the effect of surgical intervention on cognitive functions in humans has a number of difficulties, primarily ethical ones, because the creation of a group to perform an operation in children without any anesthesia is impossible. It is necessary to analyze non-surgical diagnostic and therapeutic procedures that require anesthesia in comparison with surgical interventions in future studies.

Another important issue is the impact of temporary changes in systemic homeostasis during general anesthesia on the developing brain of the child. There is evidence that changes in homeostasis, such as hypoxia/hyperoxia, hypoglycemia/hyperglycemia, changes in electrolyte composition, and low blood pressure, lead to worsening of postoperative neurological outcomes in children [27, 45]. But, there is still little information on how neurological disorders due to changes in homeostasis are related to the patient's age, duration, type of anesthesia and surgery. There are currently no studies identifying causal relationship. It is clear that new studies to investigate the impact of changes in systemic homeostasis during and after surgery on the development of the nervous system are needed.

CONCLUSION

A large amount of evidence on the neurotoxicity of anesthetics was collected animal research and clinical trials in children. However, there is currently limited information received on neurocognitive risk after of exposure to general anesthesia. The GAS, MASK, and PANDA studies have provided some preliminary conclusions that can be used in anesthesiology practice to assess the risk of postoperative cognitive dysfunction. The results of the studies showed that single and short exposure (less than 1 hour) to general anesthesia does not affect children's neurocognitive function. But, repeated exposures to anesthetics may impair some of a child's skills. Future additional studies are needed to better understand the conditions that may lead to risk. The effects of different drugs and drug combinations, impact of anesthetic dose and frequency of repeated anesthesia should be studied.

In addition, many other issues remain unsolved. There is still uncertainty regarding the effects of general anesthesia for more than one hour on the nervous system of children. The study of Professor P. Szmuk et al. on the T-REX trial should clarify this question. There is a need to identify more precise biomarkers associated with general anesthetic neurotoxicity for the assessment of intermediate outcomes. This, in turn, may resolve one of the major problems in conducting prospective studies in this field. Biomarker detection should be a promising topic for new studies in the future. It is also important to develop methods to identify anatomical damage after general anesthesia and establish a putative association with adverse neurocognitive outcomes in children. MRI seems to be one of the possible methods for detecting damage. In addition to the effect of anesthesia, new studies should also determine the role of surgery, type of surgical procedure and temporary changes in systemic homeostasis in the development of postoperative cognitive dysfunction in children.

ADDITIONAL INFORMATION

The author read and approved the final version before publication.

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