https://doi.org/10.15360/1813-9779-2023-1-2202

Etiology and Pathogenesis of Postoperative Cognitive Dysfunction (Review)

Mikhail I. Neimark, Vadim V. Shmelev,
Abdukhamid A. Rakhmonov, Zoya A. Titova*

Altai State Medical University, Ministry of Health of Russia,
40 Lenin Av., 656038 Barnaul, Altai District, Russia

For citation: *Mikhail I. Neimark, Vadim V. Shmelev, Abdukhamid A. Rakhmonov, Zoya A. Titova.* Etiology and Pathogenesis of Postoperative Cognitive Dysfunction. *Obshchaya Reanimatologiya = General Reanimatology.* 2023; 19 (1): 60–71. https://doi.org/10.15360/1813-9779-2023-1-2202 [In Russ. and Engl.]

***Correspondence to:** Zoya A. Titova, zoy.t22@yandex.ru

Summary

Impairment of higher mental functions can complicate the course of the postoperative period even after short and minimally invasive, including laparoscopic, surgical procedures. Postoperative cognitive dysfunction significantly challenges patients' quality of life, negating real success of surgical intervention and anesthetic support. In some cases, early postoperative cognitive dysfunction may be one of the main predictors of persistent cognitive impairment.

The purpose of the review. To contemplate etiology, pathogenesis and the current perspective of postoperative cognitive dysfunction.

We analyzed 96 publications in various databases (PubMed, Medline, RSCI and others), including 67 papers published over the past 5 years.

The review provides an overview of current definitions and classification of postoperative cognitive dysfunction, data on the prevalence, polyethyology and risk factors, potential impact of the type of anesthesia and surgical intervention on the development of postoperative cognitive dysfunction. Various pathogenetic mechanisms of higher mental functions impairment alongside with available effective pharmacotherapies to correct them were considered.

Conclusion. Numerous adverse factors of the perioperative period, such as neurotoxic effects of general anesthetics, neuroinflammation in response to operational stress and surgical trauma, impaired autoregulation of the cerebral blood flow, imperfect oxygen homeostasis, interactions of neurotransmitter, etc., can potentially cause postoperative cognitive dysfunction. Further deeper insights into etiology and pathogenesis of early postoperative cognitive dysfunction are relevant and necessary to improve prevention strategies and identify most effective pharmacotherapies to correct such disorders.

Keywords: postoperative cognitive dysfunction; higher mental functions; neuropsychological testing; cognitive disorders

Conflict of interest. The authors declare no conflict of interest.

Read the full-text English version at www.reanimatology.com

Introduction

Ensuring patient comfort in the perioperative period is a major challenge for modern anesthesia care [1, 2]. This issue has been interpreted in a broad sense, ranging from the elimination of emotional lability and anxiety in the preoperative period, adequate anesthetic support during surgery, effective postoperative anesthesia with early patient activation, avoidance of postoperative nausea and vomiting, muscle tremor, excessive sedation, to the prevention and elimination of cognitive dysfunction [3, 4].

Disorders of higher mental activity and development of postoperative cognitive dysfunction (POCD) significantly worsen the quality of life and negate the success of both the performed surgical intervention and the anesthetic aid. Disorders of higher mental functions (HMF) can complicate the postoperative period even after minimally invasive and short-term surgical procedures, including laparoscopic surgery. Several studies [5, 6] have shown that early POCD is one of the main predictors of persistent cognitive dysfunction.

Aim of the review. To discuss the ethology, pathogenesis, and current status of postoperative cognitive dysfunction.

Definition and Classification

In the postoperative period, patients who have undergone anesthesia and surgery may develop a variety of cognitive impairments ranging from POCD to delirium. Postoperative delirium can be defined as an acute confusion that may manifest as impaired consciousness, cognitive dysfunction, or changes in perception and behavior.

The duration of postoperative delirium can vary from a few hours to several days and should be distinguished from dementia and postoperative cognitive impairment [7].

According to L. S. Rasmussen (2001), postoperative cognitive dysfunction is a disorder that develops in the early and persists into the late postoperative period, manifesting as impaired memory, reasoning, language, and other higher cortical functions, and can be confirmed by neuropsychological

testing (NPT) as a decrease of at least 20% (or ±1SD) in postoperative scores compared to preoperative scores [8].

Currently, according to the definition of the International Working Party for Nomenclature of Perioperative Cognitive Disorders proposed at the 16th World Congress of Anaesthesiologists (Hong Kong, 2016) and subsequently endorsed in Geneva (Euroanaesthesia 2017), POCD is defined as cases in which the difference in NPT is at least ±1.96 SD from baseline values based on at least two tests from a battery of 5–10 tests [9].

Until recently, POCD was classified according to the duration of clinical manifestations as

— acute or short-term type (acute postoperative cognitive dysfunction or short-term cognitive disturbance) lasting up to 1 week after surgery;

— intermediate postoperative cognitive dysfunction lasting up to 3 months after hospital discharge;

— long-term cognitive decline or prolonged postoperative cognitive dysfunction with cognitive impairment lasting 1–2 years or longer.

Postoperative cognitive dysfunction can manifest as impaired memory and attention, speech, spatial and temporal orientation, counting, ability to think abstractly, development or worsening of depression, and can vary in severity [10, 11].

Mild cognitive impairment refers to minor changes in daily activities, primarily related to impaired memorization of new material. These «subjective» cognitive impairments do not significantly interfere with a person's daily life and may not be detected by tests because the parameters analyzed are within or slightly off the statistical average for the age group. Mild cognitive impairment is only perceived by the patient when he or she notices a deterioration in memory or responsiveness compared to his or her individual standard [12–14].

Gradually, with age, memory and thinking become weaker, and it becomes more difficult to focus attention and choose the right words. These changes are associated with natural aging and the development of moderate cognitive impairment. In some cases, they exceed the age-specific reference but do not reach the severe level of dementia. Self-referral to a doctor is one of the subjective criteria for distinguishing moderate cognitive impairment from mild dementia. When dementia develops, the patient is usually brought to the doctor by relatives. Moderate cognitive impairment significantly interferes with daily activities and memory is retained only for well-learned or personal information. The term «moderate cognitive impairment» has been included in ICD-10 as an independent entity. According to the ICD-10 recommendations, this diagnosis corresponds to:

— impaired memory, attention, or learning;

— increased fatigue with mental work;

— memory and other higher brain function abnormalities not associated with dementia or delirium;

— organic nature of the above disorders.

Moderate cognitive impairment occurs in 11–17% of older adults and is considered by neurologists to fall between the normal aging process and severe dementia. In many patients (up to 85%) with moderate cognitive impairment, memory impairment is the hallmark, but impairment of multiple cognitive functions (thinking, attention, language) can also be detected.

Moderate cognitive impairment is not a disease entity, but rather a syndrome. It may be due to different causes or a combination of them (age-related changes, neuronal death, vascular problems, metabolic disorders). Therefore, when a syndrome of moderate cognitive impairment appears, a thorough clinical and functional examination should be performed to identify its possible cause.

About half of patients complaining of memory disturbance have no evidence of cognitive impairment. The most common cause of symptoms without objective confirmation are emotional disorders such as increased anxiety or low mood, including depression [15, 16].

In severe cognitive impairment, patients are unable to remember new information or reproduce previously learned material. POCD may be reversible in some patients, and many authors consider the relationship between severe POCD and the development of dementia [17].

Dementia refers to the most severe cognitive impairment that results in an inability to function in daily life, is not associated with disorders of consciousness, and has a progressive course. Dementia is more common in the elderly, affecting at least 5% of people over the age of 65. Dementia manifests itself simultaneously in several cognitive areas, such as thinking, memory, attention, and language. Even in its early stages, the impairment is significant enough to adversely affect both daily life and work activities.

According to modern nomenclature, early POCD can be diagnosed from the 7th postoperative day. Cognitive impairment that persists up to 3 months after surgery (previously defined as «intermediate POCD») is referred to as delayed neurocognitive recovery [18].

Epidemiology

The first studies on the epidemiology of POCD were performed in 1955, when P. Bedford published in the Lancet data from a retrospective analysis of the postoperative period of 1193 elderly patients who underwent surgery under general anesthesia.

Cognitive impairment of varying severity was observed in approximately 10% of patients [19].

Similar data were obtained in a randomized study of the International Study of Post-Operative Cognitive Dysfunction (ISPOCD 1, 1998), which showed the persistence of cognitive deficit in 9.9% of patients during 3 months postoperatively. In older patients (over 75 years), persistent POCD was found in 14% of cases [20].

According to the results of the international multicenter study ISPOCD 2 (2000), the incidence of early POCD after non-cardiac surgery under general anesthesia was 19.2% in middle-aged patients (40–60 years old) and 21.4% in elderly patients, while the incidence of persistent POCD reached 6.2% [21].

In a study by T. Monk et al. [22], 1064 patients of different ages undergoing non-cardiac surgery were analyzed. NPT was performed preoperatively, at hospital discharge (4–10 days), and 3 months postoperatively according to the ISPOCD study methodology. In young patients (18–39 years) POCD was observed in 36.6% at hospital discharge and in 5.7% 3 months after surgery, in middle-aged patients (40–59 years) short-term POCD was observed in 30.4% of cases, intermediate POCD in 5.6%, while in elderly patients (60 years and older) the frequency of short-term and intermediate POCD was 41.4 and 12.7%, respectively. The authors paid special attention to the significant relationship between the history of POCD and patient survival: if the NPT indicated POCD both at hospital discharge and 3 months after surgery, mortality during the first year after surgery was significantly higher than without POCD at all study stages (10.6% vs. 2.1%, $P = 0.02$) (class of recommendations IIa, level of evidence B). The risk of persistence of POCD in the late postoperative period was higher in patients over 60 years of age, with a low level of education, and with a history of stroke [23].

A recent systematic review analyzed 7 papers with data from neuropsychological testing of 2796 patients. Tests were performed 7 days postoperatively, 3 months later, and in the long term (12–60 months). Early POCD developed in different categories of patients with a frequency ranging from 17% to 56% and a tendency to resolve later (3–34.2%). Risk factors for POCD were old age, insulin resistance and low educational level. The type of surgical procedure performed and anesthesia used did not affect the incidence of cognitive impairment [24]. In a randomized controlled trial of 60 elderly patients over 60 years of age undergoing knee replacement surgery under general anesthesia, the incidence of early POCD was 20% [25].

Etiology

Nowadays, POCD is considered to be multifactorial, with the main causes of HMF impairment being both anesthesia-related and patient-specific (including the nature of the surgery or mental/medical status) [26, 27]. In a review by N. Patel et al. [28] based on 130 randomized clinical trials, the major causes of POCD included anesthesia (15 studies), blood pressure variations (5), cerebral autoregulation disorders (4), systemic inflammatory response (26), hypothermia and rewarming (19 and 6, respectively). Other predictors of POCD include early age (less than 3 years) [29] and old age (more than 60 years), male sex, low level of education, baseline cognitive deficit, history of anxiety and depressive disorders, neurological diseases, especially of vascular etiology [30].

From the perspective of evidence-based medicine (recommendation class II, level of evidence A, B), the third trimester of pregnancy, alcoholism, genetic predisposition (epsilon 4 allele of apolipoprotein E) are also considered predictors of impaired postoperative HMF [31]. The incidence and severity of POCD are influenced by the duration and frequency of general anesthesia, especially when its duration exceeds 3.5–4 hours [32–34]. A meta-analysis of 21 randomized clinical trials by S. E. Mason et al. convincingly (OR = 1.34; 95% CI: 0.93–1.95) demonstrated an association between POCD and type of anesthesia. General anesthesia significantly increases the risk of cognitive decline compared to regional (or combined) anesthesia [35, 36]. The risk of developing cognitive impairment is significantly increased during carotid artery reconstruction, cardiac surgery [37], especially with the use of cardiopulmonary bypass. Studies by T. V. Klyp [38, 39] show the development of neurocognitive disorders of varying severity in 30–70% of patients after cardiac surgery.

Pathogenesis

Until the end of the last century, anesthetic neurotoxicity was considered the main element in the pathogenesis of brain damage. At the same time, it was noted that POCD occurs much more frequently in the elderly (over 60 years of age) than in younger patients and in children under 3 years of age. However, a large number of studies have shown that the neurotoxic effects of general anesthetic drugs are most severe in children, especially in the younger age group. The adverse effects of general anesthesia on brain structures in school-aged children result in impaired neuropsychological development both in the postoperative period and in the long term [40]. The pooled hazard ratio (HR) for children undergoing their first anesthesia before the age of four is 1.25 (95% CI: 1.13–1.38; $P < 0.001$) [41]. In 2016, the FDA indicated the potential risk of POCD with surgery lasting more than 3 hours or multiple anesthetics in children younger than 3 years and in women in the third trimester of pregnancy [42]. Recent studies have not shown a significant decrease in the incidence of POCD with

the use of modern anesthetics (sevoflurane, desflurane, etc.), which, according to most authors [43–45], have cerebro- and neuroprotective properties that outweigh possible neurotoxic effects, compared with the previous generation of anesthetics, as well as with the use of neuroaxial techniques.

Currently, the mechanism of postoperative disorders of HMF is considered to be multifactorial [46], developing under the influence of numerous unfavorable factors of the entire perioperative period [47]. The pathogenesis of POCD is based on a complex of pathophysiological changes in the central nervous system (CNS). The CNS structures where general anesthesia-induced neurodamage develops include medial septal nucleus, reticular formation, thalamic nuclei, hippocampus, neocortex (frontal, parietal, temporal, and occipital lobes), hypothalamus [48].

General anesthesia is accompanied by increased permeability of mitochondrial membranes, leading to their dysfunction, disturbs calcium homeostasis in neurons and inhibits energy processes [49]. Sevoflurane and isoflurane inhalation anesthetics can induce neuronal apoptosis due to caspase activation and aggregation toxicity of β-amyloid peptides [50]. General anesthesia for more than 1 hour causes hyperphosphorylation of tau protein, a major internal neuronal membrane protein, which directly induces brain cell death [51]. This pattern has been attributed to propofol and dexmedetomedine, which cause increased tau protein phosphorylation in the murine hippocampus in vitro [52]. In view of the above, the choice of anesthetic should clearly be aimed at minimizing its neurotoxicity. For this purpose, a comparative evaluation of different anesthetic techniques should be performed.

A meta-analysis of 15 randomized clinical trials (RCTs) involving 1854 elderly noncardiac patients showed that the incidence of early POCD was significantly lower after propofol anesthesia than after inhalational anesthesia (*RR* = 0.37; 95% CI: 0.15–0.88; *P* = 0.025), and NPT scores were significantly higher after propofol anesthesia than after inhalational anesthesia (SMD = 0.59; 95% CI: 0.07–1.11, *P* = 0.026) [53]. At the same time, in a meta-analysis of 28 RCTs with 4507 randomized participants over 60 years of age undergoing similar surgical procedures as in the previous study, there was no conclusive evidence of a benefit of propofol-based total intravenous anesthesia for reducing POCD (SMD = –0.52; 95% CI: 0.31–0.87) compared with inhalational anesthesia [54, 55].

In a Russian prospective randomized study (*N*=40) of carotid endarterectomy, cognitive decline of 2 or more MoCA (Montreal Cognitive Dysfunction Scale) points was observed in 55% (day 1) and 35% (day 5) of patients in the total intravenous propofol anesthesia group, which was significantly higher than in the sevoflurane inhalation anesthesia group, where the incidence of POCD was significantly lower (35% on day 1 and 5% on day 5) [56].

A meta-analysis of the use of ketamine as an adjunct to general anesthesia in 3 RCTs showed a lower risk of POCD (*OR* = 0.34; 95% CI: 0.15–0.73) compared with propofol-based total intravenous anesthesia [57]. A meta-analysis of 26 RCTs showed that the perioperative use of dexmedetomidine significantly reduced the incidence of POCD (OR = 0.59; 95% CI: 0.45–2.95) and improved neuropsychological test scores (MMSE) (SMD = 1.74; 95% CI: 0.43–3.05) compared to groups without its use [58].

A number of studies have examined the relationship between the incidence of POCD and the depth of hypnosis [59]. In a meta-analysis of 10 RCTs including 3142 patients, the incidence of POCD was significantly lower in the shallow anesthesia group than in the deep anesthesia group on day 1 (*RR* = 0.14; 95% CI: 0.04–0.45; *P* > 0.10) and 3 months after surgery (*RR* = 0.72; 95% CI: 0.54–0.96; *P* > 0.10) [60]. The opposite results were found in another RCT. In 66 elderly patients who underwent total knee replacement surgery under general anesthesia, the incidence of early POCD on postoperative day 7 was 20% with a bispectral index (BIS) of 40–50, whereas in the comparison group with a BIS of 55–65, the incidence was only 3.3% [61]. At the same time, a meta-analysis of 4 studies showed no significant correlation of POCD incidence between low and high BIS groups (*R* = 0.84; 95% CI: 0.21–3.45; *P* > 0.05) [62].

Some studies have analyzed the association of POCD with the quality of antinociceptive protection achieved during surgery. Antinociceptive failure leads to overexcitation and depletion of the energy balance of cortical and subcortical neurons responsible for an adequate level of consciousness [63, 64].

Intraoperative awakening may play a significant role in the development of postoperative cognitive dysfunction, which could significantly worsen patients' quality of life in the long term after surgery. Possible residual effects of components of general anesthesia, primarily anesthetics and their biotransformation products, on the CNS have been studied [65].

Studies on the effect of general anesthesia on HMF are intriguing. First of all, this concerns modern neuroaxial techniques, because in any variant of their use (alone or as a component of antinociceptive protection in combined anesthesia or for postoperative prolonged epidural analgesia), the doses of systemic drugs are significantly reduced. For example, seven RCTs involving 1,031 patients showed that the incidence of POCD was significantly lower in patients who received regional anesthesia than in those who received general anesthesia on days 1

and 3 after surgery ($P < 0.05$). However, no significant differences were found between the two types of anesthesia on day 7 and 3 months after surgery ($P > 0.05$) [66–68].

In a multicenter, randomized trial of patients over 60 years of age undergoing major noncardiac surgery, a significant reduction in POCD was found when neuroaxial anesthesia was used during the first week after surgery compared with general anesthesia. The advantages of epidural and spinal analgesia include adequate antinociceptive effect, reduced dose of general anesthetics, prevention of postoperative complications (cardiovascular, pulmonary, renal, thromboembolic, infectious), which both improve surgical treatment outcomes and contribute to the prevention of POCD and better quality of life of patients [69].

Recently, the role of neuroinflammation in the mechanisms of adverse effects of surgery on mental status has been increasingly recognized. It is caused by a systemic inflammatory response to surgical stress, inadequate postoperative anesthesia, invasive procedures, and drug therapy. The inflammatory response is accompanied by the release of potent pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) into the systemic circulation. They disrupt the integrity of the blood-brain barrier, promote the migration of macrophages and activated leukocytes into brain tissue, which is associated with the activation of microglia and astrocytes, resulting in the initiation of neuroinflammation with impaired neuronal function and the development of cognitive disorders [70–73]. This theory is supported by a meta-analysis of 13 studies showing an association between POCD and IL-6 and protein S-100, a marker of brain damage [74, 75]. In another meta-analysis of 15 RCTs involving 1854 elderly non-cardiac patients, IL-6 (SMD = –2.027; 95% CI: –3.748 to –0.307; $P = 0.021$) and TNF-α (SMD = –0.68; 95% CI: –0.93 to –0.43; $P < 0.001$) levels were significantly lower after propofol anesthesia than after inhalational anesthesia [76].

The use of dexmedetomidine contributed to the reduction in levels of key proinflammatory cytokines. A meta-analysis of 26 RCTs showed that perioperative use of dexmedetomidine significantly reduced IL-6 (SMD = –1.31; 95% CI: –1.87 to –0.75; $P < 0.001$) and TNF-α (SMD = –2.14; 95% CI: –3.14 to –1.14; $P < 0.001$) levels compared with the control group without its use [77].

Regarding the efficacy of clinical use of drugs with selective action on different brain structures, which refers to different neuroprotective agents, we did not find convincing evidence-based studies in the databases (PubMed, Medline). The results of some studies are of some practical interest and promising for the application and correction of HMF disorders caused by anesthesia and surgery.

First of all, this is true for cholinergic precursors (citicoline, gliatilin). The cholinergic system closely interacts with the dopaminergic and GABAergic systems in the CNS, providing and maintaining optimal levels of cognitive function, and its dysfunction plays a role in the development of POCD [78].

Citicoline is one of the few neuroprotectants with proven clinical efficacy that has been included in the European clinical guidelines for the treatment of ischemic stroke. A double-blind, placebo-controlled study was conducted to evaluate the efficacy of cerebral neuroprotection with citicoline during surgical procedures under general anesthesia. Neuropsychological testing on day 1 after surgery revealed POCD in 50% of patients in the comparison group, while cognitive impairment was observed in only 20% of patients in the main group ($P < 0.05$). On day 3 after surgery, long-term memory scores (according to the results of the 10-word memory test) were 56% better in the majority of patients in the study group than in the control group ($P < 0.05$) [79].

Some clinical experience is available with cytoflavin, a neurotropic antioxidant with metabolic activity. In an RCT of 60 operated school-aged children, the incidence of POCD in the cytoflavin group was 6.67% on day 1 of the postoperative period and 3.33% on day 7. In the group without cytoflavin, POCD developed in 13.79% and 27.59% of cases, respectively. The use of intraoperative metabolism-directed cerebral protection during total intravenous anesthesia based on propofol and fentanyl reduced the incidence of POCD in school-aged children by 8 times ($P < 0.01$) [40, 41].

Regarding the possible role of Cellex, a neuroprotectant with pronounced neuroplasticity, in the correction of early POCD, there are successful results of its use in patients with various neurological disorders [80, 81].

A possible imbalance of neurotransmitter (adrenergic, cholinergic, NMDA and GABAergic) interactions in the CNS, accumulation of excitatory mediators such as dopamine, seems interesting and promising [82]. Disturbed neurotransmitter interactions between dopamine and acetylcholine may cause dissociation of excitation-inhibition in the CNS. Altered production of key neurotransmitters can result from impaired delivery of neurotransmitter precursor amino acids to the brain. This can occur when the ratio of aromatic to non-aromatic amino acids in the blood changes, causing excitotoxicity of monoaminergic regulation [83]. The development of neurotransmitter disorders may potentiate the pharmacological neurotoxicity of general anesthetics. In some cases, this can lead to a a deficit of cholinergic activity with the development of central anticholinergic syndrome, which is a specific complication of general anesthesia, manifested by abnormal awakening with its slowing or severe psychomotor agitation

or intense muscle tremor, the pathogenesis of which is based on an acute deficit of central cholinergic activity. Anticholinergic drugs used in anesthesiology and intensive care mostly show selective antagonism against muscarinic receptors (atropine, scopolamine), but some have a mixed mechanism of action (antihistamines, antipsychotics, tricyclic antidepressants), while others reduce acetylcholine secretion (opiates, benzodiazepines, clonidine) [84, 85].

Surgical injury has recently been found to be capable of provoking a disturbance of iron homeostasis with its accumulation in the brain, mainly in the hippocampus. Such processes lead to cognitive impairment because excessive iron causes oxidative stress and impaired mitochondrial function. In addition, glucose metabolism is impaired and ATP production is reduced due to downregulation of key enzyme genes and protein synthesis, which can induce neuronal apoptosis [86].

POCD can develop as a result of the deleterious effects of both general (hypoxemia, reduced circulation) and local (decreased cerebral blood flow, its redistribution) hypoxia. For optimal transport and consumption of O_2 by neurons, an optimal cerebral perfusion should be maintained [87, 88]. The leading role in its maintenance belongs to cerebral perfusion pressure, the value of which is directly proportional to mean arterial pressure and inversely proportional to intracranial pressure. The latter tends to increase more frequently in severe neurosurgical situations and has a significant impact on cerebral blood flow much less frequently in routine surgical practice. Recently, several studies have addressed the impact of systemic blood pressure on cerebral perfusion and consequently on the development of POCD. A meta-analysis of 24 RCTs including 4317 patients (mean age 63 years) showed that hypertension was not significantly associated with the risk of POCD (OR = 1.01; 95% CI: 0.93 to 1.09; $P = 0.82$), although in 8 studies with participation of more than 75% of men, a 27% association of hypertension with increased risk of POCD was found (OR = 1.27; 95% CI: 1.07 to 1.49; $P = 0.005$) [89]. Another RCT included 360 patients in the low target blood pressure (BP) group and 341 participants in the high target BP group. The results showed no significant difference in the incidence of POCD between the groups (*RR* = 1.26; 95% CI: 0.76–2.08; $P = 0.37$) [90]. Three RCTs including 731 patients compared the maintenance of low systolic blood pressure (SBP) (< 80 mm Hg) and high SBP (> 80 mm Hg) during coronary artery bypass grafting. POCD developed in 6.4% of all cases. Maintaining low SBP did not reduce the incidence of POCD (95% CI: 0.277–3.688; $Z = 0.018$; $P = 0.986$). Shorter cardiopulmonary bypass time reduced the incidence of POCD regardless of target BP (95% CI: –0.949 or –0.089; $P = 0.017$) [91, 92].

Cerebral saturation monitoring, along with maintaining optimal cerebral perfusion, may also help reduce the incidence of cognitive decline. A randomized trial of 192 elderly patients in the main group and 138 in the control group after abdominal surgery showed that cerebral saturation monitoring contributed to a significant ($P = 0.020$) reduction in the incidence of early POCD [93, 94].

Obesity and its comorbidities are becoming an increasingly pressing public health issue. Often, these patients undergo surgery under general anesthesia and are thought to be at high risk for developing HMF disorders. The available studies have not convincingly confirmed this hypothesis. A meta-analysis of 1432 patients over 60 years of age with a body mass index > 30 kg/m² versus ⩽30 kg/m² showed a non-significantly higher risk of POCD (OR = 1.27; 95% CI: 0.95 to 1.70; $P = 0.10$) [95]. In 17 studies with 2725 patients (mean age 67 years), there was no association between hypercholesterolemia and the risk of POCD (OR = 0.93; 95% CI: 0.80–1.08; P = 0.34). Preoperative statin use was associated with a reduced risk of POCD in eight studies (RR = 0.81; 95% CI: 0.67–0.98; P = 0.03), but data on duration of treatment were lacking [96].

Conclusion

Postoperative cognitive dysfunction is currently an urgent clinical and social challenge. Its prevention and treatment are complicated by the multiple adverse perioperative factors that underlie its development. Neurotoxic effects of general anesthetics, systemic inflammatory response with subsequent neuroinflammation after surgical stress and trauma, impaired autoregulation of cerebral blood flow due to intraoperative hypotension, abnormal blood-brain barrier permeability as a result of reperfusion injury after major cardiac surgery and vascular interventions, disorders of metal metabolism in the brain, oxygen deficiency in the brain, and imbalance of peripheral nervous system mediators play a role in the development of disorders of higher mental functions.

The solution of this problem, which is crucial for the quality of life of surgical patients, lies in further improvement of anesthesiological support of surgical interventions, implementation of advanced monitoring methods in anesthesiological practice and thorough study of POCD pathogenesis, which will allow to determine the spectrum of effective drugs for adequate correction of postoperative disorders of higher mental functions.

References

1. *Александрович Ю.С., Акименко Т.И., Пшениснов К.В.* Послеоперационная когнитивная дисфункция — является ли она проблемой для анестезиолога-реаниматолога? *Вестник анестезиологии и реаниматологии.* 2019; 16 (4): 5–11. [*Aleksandrovich Y.S., Akimenko T.I., Pshenisnov K.V.* Postoperative cognitive dysfunction — is it a problem for the anesthesiologist-intensivist? *Messenger of Anesthesiology and Resuscitation/Vestnik Anesthesiologii i Reanimatologii* 2019; 16 (4): 5–11. (In Russ.).]. DOI: 10.21292/ 2078-5658-2019-16-4-5-11.
2. *Новицкая-Усенко Л.В.* Послеоперационная когнитивная дисфункция в практике врача-анестезиолога. Медицина неотложных состояний. 2017; 4 (83): 9–15. [*Novitskaya-Usenko L.V.* Postoperative cognitive dysfunction in an anesthesiologist's practice. *Emergency medicine /Meditsina neotlozhnikh sostoyaniy*. 2017; 4 (83): 9–15. (in Russ.)]. DOI: 10.22141/2224-0586.4.83.2017.107418.
3. *Агеева Ю.Г., Козьянина К.В.* Когнитивные дисфункции у пациентов в послеоперационном периоде. *Молодой ученый.* 2020; 43 (333): 287–291. [*Ageeva Yu.G., Kozyanina K.V.* Cognitive dysfunctions in patients in the postoperative period. Y*oung scientist/ Molodoy Ucheniy*. 2020; 43 (333): 287–291. (in Russ.).].
4. *Криштафор А.А.* Базовые принципы профилактики когнитивных расстройств и восстановление когнитивных функций при критических состояниях. *Медицина неотложных состояний.* 2018; 5 (92): 150–155. [*Krishtafor A.A.* Basic principles for prevention of cognitive disorders and restoration of cognitive functions at critical states. *Emergency medicine /Meditsina neotlozhnikh sostoyaniy*. 2018; 5 (92): 150–155. (in Russ).]. DOI: 10.22141/2224-0586.5.92. 2018.143251.
5. *Needham M. J., Webb C. E., Bryden D. C.* Postoperative cognitive dysfunction and dementia: what we need to know and do. *Br J Anaesth.* 2017; 119 (suppl_1): i115–i125. DOI: 10.1093/bja/aex354. PMID: 29161395.
6. *Sprung J., Roberts R.O., Weingarten T.N., Cavalcante A.N., Knopman D.S., Petersen R.C., Hanson A.C., Schroeder D.R., Warner D.O.* Postoperative delirium in elderly patients is associated with subsequent cognitive impairment. *Br J Anaesth.* 2017; 119 (2): 316–323. DOI: 10.1093/bja/aex130. PMID: 28854531.
7. *Киреев С.С., Бадаква Т.Л., Чуканова О.А.* Делирий в послеоперационном периоде (обзор литературы). *Вестник новых медицинских технологий.* Электронное издание. 2019; 2: 44–60. [*Kireev S.S., Badakva T.L., Chukanova O.A.* Delirium in the postoperative period (literature review). *Journal of New Medical Technologies/Vestnik Novykh Meditsinskih Tehnologiy*. Electronic edition. 2019; 2: 44–60. (in Russ.).].
8. *Rasmussen L. S., Johnson T., Kuipers H. M., Kristensen D., Siersma V. D., Vila P., Jolles J., Papaioannou A., Abildstrom H., Silverstein J. H., Bonal J.A., Raeder J., Nielsen I.K., Korttila K., Munoz L., Dodds C., Hanning C.D., Moller J.T.* Does anesthesia cause postoperative cognitive dysfunction? A randomized study of regional versus general anesthesia in 438 elderly patients. *Acta Anesth Scand*. 2003; 47 (3): 260–266. DOI: 10.1034/j.1399-6576.2003.00057.x. PMID: 12648190.
9. *Cole D. J., Kharasch E. D.* Postoperative brain function toward a better understanding and the American Society of Anesthesiologists Perioperative Brain Health Initiative. *Anesthesiology*. 2018; 129 (5): 861–863. DOI: 10.1097/ALN.0000000 000002085. PMID: 30325803.
10. *Женило В.М., Акименко Т.И., Здирук С.В., Сорочинский М.А.* Проблема синдрома послеоперационной когнитивной дисфункции в анестезиологической и хирургической службе. *Современные проблемы науки и образования.* 2017; 4: 70. [*Zhenilo V.M., Akimenko T.I., Zdiruk S.V., Sorochinsky M.A.* The problem of postoperative cognitive dysfunction syndrome in anesthesiological and surgical services. *Current Problems of Science and Education/Sovremenniye Problemy Nauki i Obrazovaniya*. 2017; 4: 70. (in Russ.).]. eLIBRARY ID: 32663092.
11. *Зозуля М.В., Ленькин А.И., Курапеев И.С., Лебединский К.М.* Послеоперационные когнитивные расстройства: патогенез, методы профилактики и лечения (обзор литературы). *Анестезиология и реаниматология.* 2019; 3: 25–33. [*Zozulya M.V., Lenkin A.I., Kurapeev I.S., Lebedinsky K.M.* Postoperative cognitive disorders: the pathogenesis, methods of prevention and treatment (literature review). *Russian Journal of Anaesthesiology and Reanimatology/ Anesteziologiya i Reanimatologiya.* 2019; 3: 25–33. (in Russ.).]. DOI: 10.17116/anaesthesiology201903125.
12. *Локшина А.Б.* Современные аспекты диагностики и лечения синдрома умеренных когнитивных расстройств. *Журнал гериатрической медицины.* 2020; 3: 199–204. [*Lokshina A.B.* Modern aspects of diagnosis and treatment of mild cognitive impairment. *Russian Journal of Geriatric Medicine/ Zhurnal Geriatricheskoy Meditsiny*. 2020; 3: 199–204. (in Russ.).] DOI: 10.37586/2686-8636-3-2020-199-204.
13. *Яхно Н.Н., Коберская Н.Н., Захаров В.В., Гришина Д.А., Локшина А.Б., Мхитарян Э.А., Посохов С.И., Савушкина И.Ю.* Влияние возраста, коморбидных сердечно-сосудистых и эмоциональных факторов на легкое когнитивное снижение в среднем, пожилом и старческом возрасте. *Неврологический журнал.* 2018; 23 (6): 309–315. [*Yakhno N.N., Koberskaya N.N., Zakharov V.V., Grishina D.A., Lokshina A.B., Mkhitaryan E.A., Posokhov S.I., Savushkina I.Yu.* The influence of age, comorbid cardiovascular and emotional factors on subtle cognitive decline in average, elderly and old age. *Neurological Journal/ Nevrologicheskiy Zhurnal.* 2018; 23 (6): 309–315. (in Russ.).]. DOI: 10.18821/1560-9545-2018-23-6-309-315.
14. *Яхно Н.Н., Фёдорова Т.С., Дамулин И.В. Щербюк А.Н., Виноградов О.А., Лаврентьев А.В.* Влияние каротидной эндартерэктомии на динамику когнитивных нарушений у пациентов с атеросклеротическим стенозом сонных артерий. *Журнал неврологии и психиатрии им. С.С. Корсакова.* 2011; 111 (3): 31–37. [*Yakhno N.N., Fedorova T.S., Damulin I.V. Shcherbiuk A.N., Vinogradov O.A., Lavrentiev A.V.* The effect of carotid endarterectomy on cognitive disturbances in patients with atherosclerotic stenosis of carotid arteries. *S.S. Korsakov Journal of Neurology and Psychiatry/ Zhurnal Nevrologii i Psikhiatrii imeni S.S. Korsakova.* 2011; 111 (3): 31–37. (in Russ.).].

15. *Мурашко Н.К., Паенок А.В., Шкляева О.П., Липко В.Й., Залесная Ю.Д., Кусткова А.С., Ингула Н.И., Кравчук Н.А., Яворский В.В., Дзюба Е.Ю., Попов А.В., Галуша А.И., Пацало Л.Н.* Алгоритм диагностики и лечения когнитивных нарушений: Метод. реком. Киев; 2013: 16. [*Murashko N.K., Paenok A.V., Shklyaeva O.P., Lipko V.Y., Zalesnaya Yu.D., Kustkova A.S., Ingula N.I., Kravchuk N.A., Yavorsky V.V., Dzyuba E.Yu., Popov A.V., Galusha A.I., Patsalo L.N.* Algorithm of diagnostics and treatment of cognitive disorders: Practical guidelines. Kiev; 2013: 16. (in Russ.).].
16. *Шнайдер Н.А., Шпрах В.В., Салмина А.Б.* Постоперационная когнитивная дисфункция (диагностика, профилактика, лечение). Красноярск: КГМА; 2005: 96. [*Schneider N.A., Shprach V.V., Salmina A.B.* Postoperative cognitive dysfunction (diagnosis, prevention, treatment). Krasnoyarsk: KSMA; 2005: 96. (in Russ.).].
17. *Fodale V., Santamaria L.B., Schifilliti D., Mandal P.K.* Anaesthetics and postoperative cognitive dysfunction: a pathological mechanism mimicking Alzheimer's disease. *Anaesthesia.* 2010; 65 (4): 388–395. DOI: 10.1111/j.1365-2044. 2010.06244.x PMID: 20136805.
18. *Овезов, А. М. Пантелеева М.В.* Послеоперационная когнитивная дисфункция В кн.: *Заболотских И.Б., Проценко Д.Н.* (ред.). Интенсивная терапия. Национальное руководство: М.: ГЭОТАР-Медиа; 2021 (1): 615–626. [*Ovezov, A.M. Panteleeva M.V.* Postoperative cognitive dysfunction In the book: *Zabolotskikh I.B., Protsenko D.N.* (ed.). Intensive care. National Guidelines: Moscow: GEOTAR-Media; 2021 (1): 615–626. (in Russ.).]. ISBN 978-5-9704-6259-1.
19. *Bedford P.D.* Adverse cerebral effects of anaesthesia on old people. *Lancet.* 1955; 269 (6884): 259–263. DOI: 10.1016/s0140-6736 (55)92689-1. PMID: 13243706.
20. *Moller J.T., Cluitmans P., Rasmussen L.S., Houx P., Rasmussen H., Canet J., Rabbitt P., Jolles J., Larsen K., Hanning C.D., Langeron O., Johnson T., Lauven P.M., Kristensen P.A., Biedler A., van Beem H., Fraidakis O., Silverstein J.H., Beneken J.E., Gravenstein J.S.* Long-term postoperative cognitive dysfunction in the elderly: ISPOCD 1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction *Lancet.* 1998; 351 (9106): 857–861. DOI: 10.1016/s0140-6736 (97)07382-0. PMID: 9525362.
21. *Rasmussen L.S., Larsen K., Houx P., Skovgaard L.T., Hanning C.D., Moller J.T.* ISPOCD group, The International Study of Postoperative Cognitive Dysfunction. The assessment of postoperative cognitive function. *Acta Anaesthesiol Scand.* 2001; 45 (3): 275–289. DOI: 10.1034/j.1399-6576.2001. 045003275.x. PMID: 11207462.
22. *Monk T.G., Weldon B.C., Garvan C.W., Dede D.E., van der Aa M.T., Heilman K.M., Gravenstein J.S.* Predictors of cognitive dysfunction after major noncardiac surgery. *Anesthesiology.* 2008; 108 (1): 18–30. DOI: 10.1097/01.anes.00002 96071. 19434.1e. PMID: 18156878.
23. *Nathan N.* Beyond emergence: understanding postoperative cognitive dysfunction (POCD). *Anesth Analg.* 2018; 127 (2): 323. DOI: 10.1213/ANE. 0000000000003598. PMID: 30028379.
24. *Czyż-Szypenbejl K., Mędrzycka-Dąbrowska W., Kwiecień-Jaguś K., Lewandowska K.* The occurrence of postoperative cognitive dysfunction (POCD) — systematic review. *Psychiatr Pol.* 2019; 53 (1): 145–160. DOI: 10.12740/PP/90648. PMID: 31008471.
25. *Hou R., Wang H., Chen L., Qiu Y., Li S.* POCD in patients receiving total knee replacement under deep vs light anesthesia: a randomized controlled trial. *Brain Behav.* 2018; 8 (2): e00910. DOI: 10.1002/ brb3.910.PMID: 29484267.
26. *Полушин Ю.С., Полушин А.Ю., Юкина Г.Ю., Кожемякина М.В.* Послеоперационная когнитивная дисфункция — что мы знаем и куда двигаться далее. *Вестник анестезиологии и реаниматологии.* 2019; 16 (1): 19–28. [*Polushin Yu.S., Polushin A.Yu., Yukina G.Yu., Kozhemyakina M.V.* Postoperative cognitive dysfunction — what we know and where we go. *Messenger of Anesthesiology and Resuscitation/Vestnik Anesthesiologii i Reanimatologii.* 2019; 16 (1): 19–28. (in Russ.).]. DOI: 10.21292/2078-5658-2019-16-1-19-28.
27. *Усенко Л.В., Криштафор А.А., Тютюнник А.Г.* Дифференцированный подход к профилактике и ранней коррекции нарушений когнитивных функций в послеоперационном периоде в зависимости от их исходного состояния. *Медицина неотложных состояний.* 2016; 4 (75): 237–238. [*Usenko L.V., Krishtafor A.A., Tyutyunnik A.G.* A differentiated approach to the prevention and early correction of cognitive impairment in the postoperative period, depending on baseline cognitive status. *Emergency medicine /Meditsina neotlozhnikh sostoyaniy.* 2016; 4 (75): 237–238. (in Russ.).].
28. *Patel N., Minhas J.S., Chung E.M.* Risk factors associated with cognitive decline after cardiac surgery: a systematic review. *Cardiovasc Psychiatry Neurol.* 2015; 2015: 370612. DOI: 10.1155/2015/370612. PMID: 26491558.
29. *Пантелеева М.В., Борисова М.Н., Овезов А.М., Лобов М.А., Луговой А.А.* Послеоперационная когнитивная дисфункция в практике педиатра. *Практика педиатра.* 2017*:* 1*:* 23–26. *[Panteleeva M.V., Borisova M.N., Ovezov A.M., Lobov M.A., Lugovoy A.A.* Postoperative cognitive dysfunction in pediatrician's practice. *Pediatrician's practice/Praktika Pediatra.* 2017*:* 1*:* 23–26. *(in Russ.).].* eLIBRARY ID: 29912106.
30. *Rundshagen I.* Postoperative cognitive dysfunction. *Dtsch Arztebl Int.* 2014; 111 (8): 119–125. DOI: 10.3238/arztebl. 2014.0119. PMID: 24622758.
31. *Cao L., Wang K., Gu T., Du B., Song J.* Association between APOE epsilon 4 allele and postoperative cognitive dysfunction: a meta-analysis. *Int J Neurosci.* 2014; 124 (7): 478–485. DOI: 10.3109/00207454. 2013.860601. PMID: 24168388.
32. *Bilotta F., Gelb A.W., Stazi E., Titi L., Paoloni F.P., Rosa G.* Pharmacological perioperative brain neuroprotection: a qualitative review of randomized clinical trials. *Br J Anaesth.* 2013; 110 (Suppl 1): i113–120. DOI: 10.1093/bja/aet059. PMID: 23562933.
33. *Evered L.A., Silbert B.S.* Postoperative cognitive dysfunction and non-cardiac surgery. *Anesth Analg.* 2018; 127 (2): 496–505. DOI: 10.1213/ANE.0000 000000003514. PMID: 29889707.

34. *Feinkohl I., Winterer G., Spies C.D., Pischon T.* Cognitive reserve and the risk of postoperative cognitive dysfunction. *Dtsch Arztebl Int.* 2017; 114 (7): 110–117. DOI: 10.3238/arztebl. 2017.0110. PMID: 28302254.
35. *Besch G., Vettoretti L., Claveau M., Boichut N., Mahr N., Bouhake Y., Liu N., Chazot T., Samain E., Pili-Floury S.* Early post-operative cognitive dysfunction after closed-loop versus manual target controlled-infusion of propofol and remifentanil in patients undergoing elective major non-cardiac surgery: protocol of the randomized controlled single-blind POCD-ELA trial. *Medicine (Baltimore).* 2018; 97 (40): e12558. DOI: 10.1097/ MD.0000000000012558. PMID: 30290615.
36. *Овезов А.М., Лобов М.А., Надькина Е.Д., Мятчин П.С., Пантелеева М.В., Князев А.В.* Церебропротекция в профилактике ранней послеоперационной когнитивной дисфункции при тотальной внутривенной анестезии. *Лечащий врач.* 2013; 3: 66. [*Ovezov A.M., Lobov M.A., Nadkina E.D., Myatchin P.S., Panteleeva M.V., Knyazev A.V.* Cerebroprotection in the prevention of early postoperative cognitive dysfunction with total intravenous anesthesia. *The Attending Physician/ Lechaschiy Vrach.* 2013; 3: 66. (in Russ.).]. eLIBRARY ID: 21809448.
37. *Zhao Q., Gao R., Liu C., Chen H., Zhang X., Guan J., Xie X., Qiu Y., Cheng X., Lv P., Zhu T., Chen C.* Dynamic change of lymphocyte-to-monocyte is associated with the occurrence of POCD after cardiovascular surgery: a prospective observational study. *Front Behav Neurosci.* 2021; 15: 646528. DOI: 10.3389/fnbeh.2021.646528. PMID: 33927600.
38. *Клыпа Т.В., Антонов И.О., Вавакин А.С.* Динамика когнитивного статуса кардиохирургических больных и предикторы его нарушения. *Анестезиология и реаниматология.* 2016; 61 (1): 18–23. [*Klypa T.V., Antonov I.O., Vavakin A.S.* The cognitive status dynamic of cardiosurgical patients and the predictors of its disturbance. *Anesthesiol.Reanimatol/ Anesteziologiya i Reanimatologiya.* 2016; 61 (1): 18–23. (in Russ.).] DOI: 10.18821/0201-7563-2016-61-1-18-23.
39. *Клыпа Т.В., Шепелюк А.Н., Еременко А.А., Антонов И.О., Кричевский Л.А.* Факторы риска развития когнитивной дисфункции после кардиохирургических операций. *Кардиология и сердечно-сосудистая хирургия.* 2017; 10 (1): 62–78. [*Klypa T.V., Shepelyuk A.N., Eremenko A.A., Antonov I.O., Krichevsky L.A.* Risk factors for cognitive dysfunction after cardiac surgery. *Cardiology and Cardiovascular Surgery/Kardiologiya i Serdechno-Sosudistaya Khirurgiya.* 2017; 10 (1): 62–78. (in Russ.).] DOI: 10.17116/kardio201710162-70.
40. *Овезов А.М., Пантелеева М.В., Луговой А.В.* Интраоперационная церебропротекция при тотальной внутривенной анестезии у детей школьного возраста. *Журнал неврологии и психиатрии им. С.С. Корсакова.* 2017; 117 (10): 28–33. [*Ovezov A.M., Panteleeva M.V., Lugovoy A.V.* Intraoperative cerebroprotection in total intravenous anesthesia in children of school-age. *S.S. Korsakov Journal of Neurology and Psychiatry/ Zhurnal Nevrologii i Psikhiatrii imeni S.S. Korsakova.* 2017; 117 (10): 28–33. (in Russ.).].DOI: 10.17116/jnevro201711710128-33.
41. *Луговой А.В., Пантелеева М.В., Надькина Е.Д., Овезов А.М.* Интраоперационная профилактика когнитивных нарушений при тотальной внутривенной анестезии у детей школьного возраста: рандомизированное клиническое исследование. *Вестник интенсивной терапии имени А.И. Салтанова.* 2018; 4: 57–64. [*Lugovoy A.V., Panteleeva M.V., Nadkina E.D., Ovezov A.M.* Intraoperative prevention of cognitive impairment in total intravenous anesthesia in school-age children: a randomized clinical trial. *Ann Crit Care./Annals of Critical Care / Vestnik Intensivnoy Terapii im AI Saltanova.* 2018; 4: 57–64. (in Russ.).] DOI: 10. 21320/1818-474X-2018-4-57-64.
42. *Пантелеева М.В., Овезов А.М., Котов А.С., Луговой А.В., Князев А.В.* Послеоперационная когнитивная дисфункция у детей (обзор литературы). *Российский медицинский журнал.* 2018; 26 (9): 52–56. [*Panteleeva M.V., Ovezov A.M., Kotov A.S., Lugovoy A.V., Knyazev A.V.* Postoperative cognitive dysfunction in children (literature review). *Russian Medical Journal/ Rossiyskiy Meditsinskiy Zhurnal.* 2018; 26 (9): 52–56. (in Russ.).]. eLIBRARY ID: 35663827.
43. *Вислобоков А.И., Полушин Ю.С., Полушин А.Ю., Алферова В.В.* Изменения электрофизиологических свойств нейронов под влиянием севофлурана и их роль в механизмах прекондиционирования и цитопротекции. *Вестник анестезиологии и реаниматологии.* 2015; 12 (3): 19. [*Vislobokov A.I., Polushin Yu.S., Polushin A.Yu., Alferova V.V.* The changes of the electrophysiological properties of neurons by the action of sevoflurane and their role in the mechanisms of preconditioning and cytoprotection. *Messenger of Anesthesiology and Resuscitation/Vestnik Anesthesiologii i Reanimatologii.* 2015; 12 (3): 19. (Russ.)]. eLIBRARY ID: 23574249.
44. *Козырев А.С., Александрович Ю.С., Залетина А.В., Иванов М.Д., Павлова М.С., Стрельникова А.С.* Сравнительная оценка анестезии десфлураном и севофлураном при хирургической коррекции позвоночно-спинномозговой травмы у детей. *Ортопедия, травматология и восстановительная хирургия детского возраста.* 2018; 6 (3): 47–55. [*Kozyrev A.S., Alexandrovich Yu.S., Zaletina A.V., Ivanov M.D., Pavlova M.S., Strelnikova A.S.* Comparative of desflurane and sevoflurane anesthesia during surgical correction of vertebral and spinal cord injury in children. *Pediatric Orthopedics, Traumatology and Reconstructive Surgery/ Ortopediya, Travmatologiya i Vosstanovitelnaya Hirurgiya Detskogo Vozrasta.* 2018; 6 (3): 47–55. (in Russ.)]. DOI: 10.17816/PTORS6347-55.
45. Лебединский К.М., Коваленко А.Н. Физические и физиологические механизмы сознания и общей анестезии (Обзор). *Журнал технической физики.* 2018; 88 (10): 1443–1456. [*Lebedinsky K.M., Kovalenko A.N.* Physical and physiological mechanisms of consciousness and general anesthesia (Review). *Journal of Technical Physics/Zhurnal Tehnicheskoy Fiziki.* 2018; 88 (10): 1443–1456. (in Russ.).] DOI: 10.21883/JTF.2018.10.46484.67.
46. *Salii I., Salii M.* Postoperative cognitive dysfunction. *Norwegian Journal of development of the International Science.* 2021; 65–1: 47–41. DOI: 10.24412/3453-9875-2021-65-1-41-47.
47. *Ковальчук В.В.* Основные теоретические и практические аспекты нейрореабилитации. *Эффек-*

тивная фармакотерапия. 2018; 24: 10–23. [*Kovalchuk V.V.* Basic theoretical and practical aspects of neurorehabilitation. *Effective pharmacotherapy/ Effectivnaya pharmacotherapya*. 2018; 24: 10–23. (in Russ.)]. eLIBRARY ID: 36309376.

48. *Грицук С.Ф.* Структурно-функциональные взаимосвязи сознания и бессознательного (наркоз) в фокусе когнитивных нарушений. *Вестник интенсивной терапии имени А.И. Салтанова*. 2018; 4: 80–85. [*Gritsuk S.F.* Structural and functional relationship of consciousness and the unconscious (anesthesia) in the focus of cognitive impairment. *Ann Crit Care./ Vestnik intensivnoy terapii im AI Saltanova*. 2018; 4: 80–85. (in Russ).]. DOI: 10.21320/18-474 X-2018-4-80-85.
49. *Овезов А.М., Пантелеева М.В., Князев А.В., Луговой А.В., Брагина С.В.* Когнитивная дисфункция и общая анестезия: от патогенеза к профилактике и коррекции. *Неврология, нейропсихиатрия, психосоматика*. 2016; 8 (3): 101–105. [*Ovezov A.M., Panteleeva M.V., Knyazev A.V., Lugovoy A.V., Bragina S.V.* Cognitive dysfunction and general anesthesia: from pathogenesis to prevention and correction. *Neurology, neuropsychiatry, psychosomatics/ Nevrologiya Neiropsikhiatriya, Psikhosomatika*. 2016; 8 (3): 101–105. (in Russ.).] DOI: 10.14412/2074-2711-2016-3-101-105.
50. *Dong Y., Zhang G., Zhang B., Moir R.D., Xia W., Marcantonio E.R., Culley D.J., Crosby G., Tanzi R.E., Xie Z.* The common inhalational anesthetic sevoflurane induces apoptosis and increases beta-amyloid protein levels. *Arch Neurol*. 2009; 66 (5): 620-631. DOI: 10.1001/archneurol.2009.48. PMID: 19433662.
51. *Xie Z., Dong Y., Maeda U., Alfille P., Culley D.J., Crosby G., Tanzi R.E.* The common inhalation anesthetic isoflurane induces apoptosis and increases amyloid beta protein levels. *Anesthesiology*. 2006; 104 (5): 988–994. DOI: 10.1097/00000542-200605000-00015. PMID: 16645451.
52. *Whittington R.A., Virág L., Marcouiller F., Papon M.A., El Khoury N.B., Julien C., Morin F., Emala C.W., Planel E.* Propofol directly increases tau phosphorylation. *PLOS One*. 2011; 6 (1): e16648. DOI: 10.1371/journal.pone.0016648. PMID: 21304998.
53. *Pang Q.Y., Duan L.P., Jiang Y., Liu H.L.* Effects of inhalation and propofol anaesthesia on postoperative cognitive dysfunction in elderly noncardiac surgical patients: a systematic review and meta-analysis. *Medicine (Baltimore)*. 2021; 100 (43): e27668. DOI: 10.1097/MD.0000000000027668. PMID: 34713863.
54. *Geng Y-J., Wu Q-H., Zhang R-Q.* Effect of propofol, sevoflurane, and isoflurane on postoperative cognitive dysfunction following laparoscopic cholecystectomy in elderly patients: a randomized controlled trial. *J Clin Anesth*. 2017; 38: 165–171. DOI: 10.1016/ j.jclinane.2017.02.007. PMID: 28372661.
55. *Miller D., Lewis S.R., Pritchard M.W., Schofield-Robinson O.J., Shelton C.L., Alderson P., Smith A.F.* Intravenous versus inhalational maintenance of anaesthesia for postoperative cognitive outcomes in elderly people undergoing non-cardiac surgery. *Cochrane Database Syst Rev*. 2018; 8 (8): CD012317. DOI: 10.1002/14651858.CD012317.pub2. PMID: 30129968.
56. *Образцов М.Ю., Кузьков В.В., Киров М.Ю, Иващенко О.Ю., Иващенко Н.Ю., Анисимов М.Г., Горенько В.М.* Влияние типа анестезии на церебральную оксигенацию и когнитивные функции при каротидной эндартерэктомии. *Вестник анестезиологии и реаниматологии*. 2017; 14 (1): 3–12. [*Obraztsov M.Yu., Kuzkov V.V., Kirov M.Yu., Ivashchenko O.Yu., Ivashchenko N.Yu., Anisimov M.G., Gorenkov V.M.* The effect of anesthesia type on cerebral oxygenation and cognitive functions in carotid endarterectomy. *Messenger of Anesthesiology and Resuscitation/Vestnik Anesthesiologii i Reanimatologii*, 2017; 14 (1): 3–12. (in Russ.).] DOI 10.21292/2078-5658-2017-14-1-3-13.
57. *Hovaguimian F., Tschopp C., Beck-Schimmer B., Puhan M.* Intraoperative ketamine administration to prevent delirium or postoperative cognitive dysfunction: a systematic review and meta-analysis. *Acta Anaesthesiol Scand*. 2018; 62 (9); 1182–1193. DOI: 10.1111/aas.13168. PMID: 29947091.
58. *Bi X., Wei J., Zhang X.* Effects of dexmedetomidine on neurocognitive disturbance after elective noncardiac surgery in senile patients: a systematic review and meta-analysis. *J Int Med Res*.2021; 49 (5): 3000605211014294. DOI: 10.1177/03000605211014294. PMID: 33983077.
59. *Badenes R., Garcia-Perez M.L., Bilotta F.* Intraoperative monitoring of cerebral oximetry and depth of anaesthesia during neuroanesthesia procedures. *Curr Opin Anaesthesiol*. 2016; 29: 576–581. DOI: 10.1097/ACO.0000000000000371. PMID: 27367415.
60. *Li Y., Zhang B.* Effects of anesthesia depth on postoperative cognitive function and inflammation: a systematic review and meta-analysis. *Minerva Anestesiol*. 2020; 86 (9): 965–973. DOI: 10.23736/S0375-9393.20.14251-2. PMID: 32251571.
61. *Ballard C., Jones E., Gauge N., Aarsland D., Nilsen O.B., Saxby B.K., Lowery D., Corbett A., Wesnes K., Katsaiti E., Arden J., Amoako D., Prophet N., Purushothaman B., Green D.* Optimised anaesthesia to reduce post operative cognitive decline (POCD) in older patients undergoing elective surgery, a randomised controlled trial. *PLoS One*. 2012; 7 (6): e37410. DOI: 10.1371/journal.pone.0037410. PMID: 22719840.
62. *Lu X., Jin X., Yang S., Xia Y.* The correlation of the depth of anesthesia and postoperative cognitive impairment: a meta-analysis based on randomized controlled trials. *J Clin Anesth*. 2018; 45: 55–59. DOI: 10.1016/j.jclinane.2017.12.002. PMID: 29275267.
63. *Акименко Т.И.* Эмоционально-психические и когнитивные расстройства в практике анестезиолога-реаниматолога. *Медицина: теория и практика*. 2018; 3 (4): 19–26. [*Akimenko T.I.* Emotionally mental and cognitive disorders in the practice of anesthesiologist-reanimatologist. *Medicine: Theory and Practice/Meditsina: Teoriya i Praktika*. 2018; 3 (4): 19–26. (in Russ.).] eLIBRARY ID: 37105248.
64. *Белозерцева И.В., Драволина О.А., Кривов В.О., Тур М.А., Мус Л.В., Полушин Ю.С.* Послеоперационные изменения поведения крыс, получавших анестезию севофлураном. *Вестник анестезиологии и реаниматологии*. 2017; 14 (2): 55–63. [*Belozertseva I.V., Dravolina O.A., Krivov V.O., Tur M.A., Mus L.V., Polushin Yu.S.* Postoperative changes in the behavior of rats after anesthesia with sevoflu-

rane. *Messenger of Anesthesiology and Resuscitation/ Vestnik Anesthesiologii i Reanimatologii*. 2017; 14 (2): 55–63. (in Russ.).] DOI 10.21292/2078-5658-2017-14-2-55-63.

65. *Bocskai T., Kovács M., Szakács Z., Gede N., Hegyi P., Varga G., Pap I., Tóth I., Révész P., Szanyi I., Németh A., Gerlinger I., Karádi K., Lujber L.* Is the bispectral index monitoring protective against postoperative cognitive decline? A systematic review with meta-analysis. *PLoS One*. 2020; 15 (2): e0229018. DOI: 10.1371/journal.pone.0229018. PMID: 32053678.
66. *Акименко Т.И., Женило В.М., Лебедева Е.А., Здирук С.В., Александрович Ю.С.* Влияние интраоперационной седации при ампутации матки в условиях спинальной анестезии на когнитивные функции в послеоперационном периоде. *Вестник анестезиологии и реаниматологии*. 2018; 15 (1): 10–17. [*Akimenko T.I., Zhenilo V.M., Lebedeva E.A., Zdiruk S.V., Alexandrovich Yu.S.* Impact of intraoperative sedation with spinal anesthesia during uterine amputation on cognitive functions in the postoperative period. *Messenger of Anesthesiology and Resuscitation/Vestnik Anesthesiologii i Reanimatologii*. 2018; 15 (1): 10–17. (in Russ.).] DOI 10.21292/2078-5658-2018-15-1-10-17.
67. *Соколов С.В., Заболотский Д.В.* Когнитивные дисфункции у ортопедических больных. *Российские биомедицинский исследования*. 2020; 5 (2): 49-51. [*Sokolov S.V., Zabolotsky D.V.* Cognitive dysfunctions in orthopedic patients. *Russian Biomedical Research/ Rossiyskiye Biomeditsinskiye Issledovaniya*. 2020; 5 (2): 49-51. (in Russ.)]. http: //ojs3.gpmu.org/index.php/biomedical-research/article/view/2409.
68. *Gao Y., Liu L., Zhao B., Wang Y., Yu S., Wang H.* Effect of general and non-general anesthesia on postoperative cognitive dysfunction. *J Coll Physicians Surg Pak*. 2021; 30 (4): 407–411. DOI: 10.29271/jcpsp.2020.04.407. PMID: 32513362.
69. *Страшнов В.И., Забродин О.Н.* К механизмам защитных эффектов регионарной анестезии в отношении развития послеоперационной когнитивной дисфункции. *Reviews по клинической фармакологии и лекарственной терапии*. 2018; 16 (2): 62–68. [*Strashnov V.I., Zabrodin O.N.* To the mechanisms of the protective effects of regional anesthesia in relation to the development of postoperative cognitive dysfunction. *Reviews on Clinical Pharmacology and Drug Therapy/Obzory po Klinicheskoy Farmakologii I Lekarstvennoy Terapii* 2018; 16 (2): 62–68. (in Russ.).]. DOI: 10.17816/RCF16262-68.
70. *Alam A., Hana Z., Jin Z., Suen K.C., Ma D.* Surgery, neuroinflammation and cognitive impairment. *EBioMedicine*. 2018; 37: 547–556. DOI: 10.1016/j.ebiom.2018.10.021 PMID: 30348620.
71. *Wiberg S., Holmgaard F., Zetterberg H., Nilsson J.C., Kjaergaard J., Wanscher M., Langkilde A.R., Hassager C., Rasmussen L.S., Blennow K., Vedel A.G.* Biomarkers of cerebral injury for prediction of postoperative cognitive dysfunction in patients undergoing cardiac surgery. *J Cardiothorac Vasc Anesth*. 2022; 36 (1): 125–132. DOI: 10.1053/j.jvca.2021.05.016. PMID: 34130895.
72. *Xu J., Dong H., Qian Q., Zhang X., Wang Y., Jin W., Qian Y.* Astrocyte-derived CCL2 participates in surgery-induced cognitive dysfunction and neuroinflammation via evoking microglia activation. *Behav Brain Res*. 2017; 332: 145–-153. DOI: 10.1016/j.bbr.2017.05.066. PMID: 28587818.
73. *Liu X., Yu Y., Zhu S.* Inflammatory markers in postoperative delirium (POD) and cognitive dysfunction (POCD): a metaanalysis of observational studies. *PLoS One*. 2018; 13 (4): e0195659. DOI: 10.1371/journal.pone.0195659. PMID: 29641605.
74. *Fan C.H., Peng B., Zhang F.C.* The postoperative effect of sevoflurane inhalational anesthesia on cognitive function and inflammatory response of pediatric patients. *Eur Rev Med Pharmacol Sci*. 2018; 22 (12): 3971–3975. DOI: 10.26355/eurrev_201806_15281. PMID: 29949172.
75. *Peng L., Xu L., Ouyang W.* Role of peripheral inflammatory markers in postoperative cognitive dysfunction (POCD): a meta-analysis. *PLoS One*. 2013; 8 (11): e79624. DOI: 10.1371/journal.pone.0079624. PMID: 24236147.
76. *Liu X., Yu Y., Zhu S.* Inflammatory markers in postoperative delirium (POD) and cognitive dysfunction (POCD): a meta-analysis of observational studies. *PLoS One*. 2018; 13 (4): e0195659. DOI: 10.1371/journal.pone.0195659. PMID: 29641605.
77. *Yang W., Kong L.S., Zhu X.X., Wang R.X., Liu Y., Chen L.R.* Effect of dexmedetomidine on postoperative cognitive dysfunction and inflammation in patients after general anaesthesia: a PRISMA-compliant systematic review and meta-analysis. *Medicine (Baltimore)*. 2019; 98 (18): e15383. DOI: 10.1097/MD.0000000000015383. PMID: 31045788.
78. *Parnetti L., Mignini F., Tomassoni D., Traini E., Amenta F.* Cholinergic precursors in the treatment of cognitive impairment of vascular origin: ineffective approaches or need for re-evaluation? *J Neurol Sci*. 2007; 257 (1–2): 264–269. DOI: 10.1016/j.jns.2007.01.043. PMID: 17331541.
79. *Овезов А.М., Лобов М. А., Надькина Е. Д., Мятчин П. С., Пантелеева М. В., Князев А. В.* Цитиколин в профилактике послеоперационной когнитивной дисфункции при тотальной внутривенной анестезии. *Анналы клинической и экспериментальной неврологии*. 2013; 7 (2): 27–33. [*Ovezov A.M., Lobov M. A., Nadkina E. D., Myachin P. S., Panteleeva M. V., Knyazev A.V.* Citicoline in the prevention of postoperative cognitive dysfunction after total intravenous anesthesia. *Annals of Clinical and Experimental Neurology/Annaly Klinicheskoy i Eksperimentalnoy Nevrologii*. 2013; 7 (2): 27–33. (in Russ.)]. DOI: 10.17816/psaic238.
80. *Ивонина Н.А., Петров К.Б., Филимонов С.Н.* Клинический опыт применения препарата Целлекс у пациентов с вестибулярным синдромом. *Медицина в Кузбассе*. 2021; 4: 26–31. [*Ivonina N.A., Petrov K.B., Filimonov S.N.* Clinical experience of using the drug Cellex in patients with vestibular syndrome. *Medicine in Kuzbass/ Meditsina v Kuzbasse*. 2021; 4: 26–31. (in Russ.).].
81. *Камчатнов П.Р., Измайлов И.А., Соколов М.А.* Результаты применения препарата Целлекс у больных с цереброваскулярными заболеваниями. *Нервные болезни*. 2018; 1: 26–31. [*Kamchatnov P.R., Izmailov I.A., Sokolov M.A.* Results of cerebrovascular

diseases treatment with Cellex. *Nervous diseases/ Nervnie bolezni*. 2018; 1: 26–31. (in Russ.).]. DOI: 10.24411/2071-5315-2018-11994.
82. *Tian M., Zhou Y., Qiu L., Liu F., Jin L., Li W., Zhang L.* NL1 expression level in Nrx1β and the excitability of PV interneurons in mice with POCD. *Exp Ther Med*. 2019; 17 (4): 3117–3123. DOI: 10.3892/etm.2019.7322. PMID: 30936983.
83. *Trzepacz P.T.* Is there a final common neural pathway in delirium? Focus on acetylcholine and dopamine. *Semin Clin Neuropsychiatry*. 2000; 5 (2): 132–148. DOI: 10.153/SCNP0 0500132. PMID: 10837102.
84. *Federico A., Tamburin S., Maier A., Faccini M., Casari R., Morbioli L., Lugoboni F.* Multifocal cognitive dysfunction in high-dose benzodiazepine users: a cross-sectional study. *Neurol Sci*. 2017; 38 (1): 137–142. DOI: 10.1007/s10072-016-2732-5. PMID: 27730361.
85. *Зозуля М.В., Ленькин А.И., Курапеев И.С., Лебединский К.М.* Послеоперационные когнитивные расстройства: патогенез, методы профилактики и лечения (обзор литературы). *Анестезиология и реаниматология*. 2019; 3: 25–33. [*Zozulya M.V., Lenkin A.I., Kurapeev I.S., Lebedinsky K.M.* Postoperative cognitive disorders: the pathogenesis, methods of prevention and treatment (literature review). *Russian Journal of Anaesthesiology and Reanimatology/ Anesteziologiya i Reanimatologiya*. 2019; 3: 25–33. (in Russ.).]. DOI: 10.17116/anaesthesiology201903125.
86. *Ge X., Zuo Y., Xie J., Li X., Li Y., Thirupathi A., Yu P., Gao G., Zhou C., Chang Y., Shi Z.* A new mechanism of POCD caused by sevoflurane in mice: cognitive impairment induced by cross-dysfunction of iron and glucose metabolism. *Aging (Albany NY)*. 2021; 13 (18): 22375–22389. DOI: 10.18632/ aging.203544. PMID: 34547719.
87. *Snyder B., Simone S.M., Giovannetti T., Floyd T.F.* Cerebral hypoxia: its role in age-related chronic and acute cognitive dysfunction. *Anesth Analg*. 2021; 132 (6): 1502–1513. DOI: 10.1213/ANE.0000000000005525. PMID: 33780389.
88. *Zorrilla-Vaca A., Healy R., Grant M.C., Joshi B., Rivera-Lara L., Brown C., Mirski M.A.* Intraoperative cerebral oximetry-based management for optimizing perioperative outcomes: a meta-analysis of randomized controlled trials. *Can J Anaesth*. 2021; 65 (5): 529–542. DOI: 10.1007/s12630-018-1065-7. PMID: 29427259.
89. *Feinkohl I., Winterer G., Pischon T.* Hypertension and risk of post-operative cognitive dysfunction (POCD): a systematic review and meta-analysis. *Clin Pract Epidemiol Ment Health*. 2017; 13: 27–42. DOI: 10.2174/1745017901713010027. PMID: 28603544.
90. *Feng X., Hu J., Hua F., Zhang J., Zhang L., Xu G.* The correlation of intraoperative hypotension and post-operative cognitive impairment: a meta-analysis of randomized controlled trials. *BMC Anesthesiol*. 2021; 20 (1): 193. DOI: 10.1186/s12871-020-01097-5. PMID: 32758153.
91. *Kiabi F.H., Soleimani A., Habibi M.R.* Neuroprotective effect of low mean arterial pressure on postoperative cognitive deficit attenuated by prolonged coronary artery bypass time: a meta-analysis. *Braz J Cardiovasc Surg*. 2021; 34 (6): 739–748. DOI: 10.21470/1678-9741-2018-0263. PMID: 31241875.
92. *Sauër A.C., Veldhuijzen D.S., Ottens T.H., Slooter A.J.C., Kalkman C.J, van Dijk D.* The association between delirium and cognitive change after cardiac surgery. *Br J Anaesth*. 2017; 119 (2): 308–315. DOI: 10.1093/bja/aex053. PMID: 28854542.
93. *Lei L., Katznelson R., Fedorko L., Carroll J., Poonawala H., Machina M., Styra R., Rao V., Djaiani G.* Cerebral oximetry and postoperative delirium after cardiac surgery: a randomised, controlled trial. *Anaesthesia*. 2017; 72 (12): 1456–1466. DOI: 10.1111/anae.14056. PMID: 28940368.
94. *Badenes R., García-Pérez M.L., Bilotta F.* Intraoperative monitoring of cerebral oximetry and depth of anaesthesia during neuroanesthesia procedures. *Curr Opin Anaesthesiol*. 2016; 29 (5): 576–581. DOI: 10.1097/ACO.0000000000000371. PMID: 27367415.
95. *Feinkohl I., Winterer G., Pischon T.* Obesity and post-operative cognitive dysfunction: a systematic review and meta-analysis. *Diabetes Metab Res Rev*. 2016; 32 (6): 643–651. DOI: 10.1002/ dmrr.2786. PMID: 26890984.
96. *Feinkohl I., Winterer G., Pischon T.* Associations of dyslipidaemia and lipid-lowering treatment with risk of postoperative cognitive dysfunction: a systematic review and meta-analysis. *J Epidemiol Community Health*. 2018; 72 (6): 499–506. DOI: 10.1136/jech-2017-210338. PMID: 29437865.

Received 09.04.2022
Accepted 20.12.2022