Choice of Anesthesia for Orthopedic Surgery in Elderly and Senile Patients (Review)

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Выбор метода анестезиологического обеспечения у пациентов пожилого и старческого возраста при ортопедических вмешательствах (обзор)

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Summary

Management of elderly and senile patients is a major challenge due to significant comorbidity, especially in surgery under general anesthesia.

The aim of the review was to identify the optimal method of anesthesia for knee arthroplasty in elderly patients based on the available clinical and experimental studies.

We searched PubMed, Medline, and Elibrary.ru databases for relevant sources. Out of more than 300 publications initially analyzed, 113 literature sources (dating from 1951 to 2021) were included in the review, of which 80 were published within the last five years (2016–2021). The inclusion criteria were high informative value and relevance, except for sources cited as historical references. Both randomized multicenter studies and individual case reports were included in the review. Exclusion criteria were low informative value, outdated and repetitive data.

We reviewed the physiology of elderly and senile patients, various variants of anesthesia, the use of neuroaxial anesthesia and peripheral regional blocks, xenon-based general anesthesia, assessed the advantages and drawbacks of each method, and discussed the monitoring of the depth of anesthesia and the issues of inraoperative awareness during knee arthroplasty in elderly and senile patients.

Conclusion. The choice of anesthesia for knee arthroplasty in elderly and senile patients should be based on the risks of decompensation of cardiovascular comorbidities and cognitive impairment. No known anesthetic method is ideal in terms of safety. The use of xenon as the main anesthetic seems promising due to its cardio- and neuroprotective properties. However, its use is limited due to relatively high cost. Therefore, the search for optimal (lower than recommended) inhalation concentrations may lead to expanding use of xenon in elderly and senile patients. At the same time, the use of lower concentrations of the drug is associated with the intraoperative awakening and the need for its combination with narcotic analgesics or amnestic agents, which may not be optimal. In addition, the protective effect of xenon retrograde amnesia against the stress of unintended intraoperative awakening has not been studied, and routine methods of monitoring the depth of hypnosis when using xenon often yield skewed measurement results inconsistent with the clinical manifestations of anesthesia.

Therefore, there is a need for further studies concerning the retrograde amnesic effect of xenon and search for optimal methods of assessing the depth of hypnosis when using this gas to safely reduce its inhalation concentration.

Keywords: xenon; EEG; monitoring the depth of hypnosis; intraoperative awakening; knee arthroplasty; anesthesia safety

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Introduction

The aging of the world's population is steadily increasing. According to the United Nations (UN), by 2050 there will be more than 1 billion people over the age of 60 [1]. In Russia, the average life expectancy in 2019 was 67.8 years for men and 72.9 years for women [2]. Another trend is an increase in the number of patients with degenerative and destructive diseases of large joints of the lower extremities, including osteoarthritis of the knee joints being a leading codition associated with activity limitation and disability [3–5]. According to current estimates, 18% of women and about 10% of men in the older age group have knee osteoarthritis, including severe one. Surgical intervention remains the most effective treatment option. Knee arthroplasty is a highly traumatic procedure which is often associated with severe pain in the postoperative period [6]. Medical management of such patients can be challenging due to multiple comorbidities, which is particularly true for surgical interventions under general anesthesia [7,8]. Therefore, the choice of anesthesia method is a major task helping select the safest possible technique with minimal risk of decompensation of comorbidities. The search for optimal anesthesia support for knee arthroplasty in elderly patients is still under way, and the problem has not yet been fully solved [6, 9, 10].

The aim of the review was to identify the optimal method of anesthesia in knee arthroplasty in elderly patients based on the available clinical and experimental studies.

We searched for sources in PubMed, Medline, and Elibrary.ru databases. From over 300 publications, 113 literature sources (dating from 1951 to 2021) were included in the review, of which 80 papers were published in 2016-2021. The inclusion criteria were high informative value and relevance, except for the sources cited as historical references. Both randomized multicenter studies and individual case reports were included in the review. Exclusion criteria were low informative value, outdated and repetitive data.

Physiological Characteristics of Elderly and Senile Patients

When planning anesthesia in elderly and senile patients, the physiology of the elderly organism should be considered together with the specific pharmacokinetics and pharmacodynamics of drugs used in the perioperative period.

More than 30% of patients in the older age group have three to five comorbidities. Age-related decline in body functions is inherent to aging and occurs at a rate of approximately 1% per year after the age of 40. There is a gradual decrease in the body reactivity, which in turn limits the adequate physiological response to stress factors, including surgical intervention, anesthesia, as well as preoperative preparation [11]. Age-related cardiac changes include impaired diastolic function and left ventricular hypertrophy, reduced number of cardiomyocytes, focal dystrophy of muscle fibers, increased connective tissue, reduced activity of sinus node, slower impulse conduction through interatrial septum, which can lead to reduced ejection fraction and arrhythmias. Sensitivity to catecholamines and acetylcholine increases, which can also provoke arrhythmias. In the elderly, reduced baroreceptor sensitivity and altered sensitivity to angiotensin II can result in a failure to adequately respond to intraoperative changes in blood pressure and hypovolemia. Increased arterial stiffness increases is associated with age-related destruction of collagen and elastin. Low exercise tolerance is essential when the ejection fraction can still be preserved, but drops on physical load due tio inability of the myocardium to fully respond by increasing the rate and contractility in accordance to the end-diastolic volume (volemia). Thus, the risk of ischemic organ and tissue damage increases [8, 11]. Decline of pulmonary function occurs mainly due to the reduction of pulmonary compliance and the number of elastic elements in lungs, resulting in increased risk of expiratory collapse of small bronchioles which causes an increase of dead space, reduction of diffusion capacity, and impaired gas exchange [8, 11]. Changes in the kidneys of older patients include their weight reduction up to 35%, loss of urine concentration and dilution capacity, caused by atrophy, mainly of cortical layer, and reduction of the number of active glomeruli. The ability to regulate sodium metabolism decreases, which leads to increased sodium retention and accumulation of fluid in the intercellular space. Renal dysfunction can also be associated with the nephrotoxic effect of long-term medications (nonsteroidal anti-inflammatory drugs, ACE inhibitors) [12]. There is a slowdown of drug biotransformation due to age-related atrophy of the liver parenchyma and reduction in the number of active hepatocytes, decreased enzyme activity and slowed metabolism with the hepatic blood flow reducing by 10% every 10 years after the age of 50. Activity of cytochrome P-450 enzymes, phase I and phase II nonmycrosomal oxidation enzymes of hepatic metabolism is impaired, resulting in a hepatic extraction clearance decrease of up to 40% [12].

Impaired cerebral vascular function, reduced concentration of such neurotransmitters as dopamine, acetylcholine, norepinephrine and serotonin contribute significantly to the development of delirium and cognitive impairment in the postoperative period. In the elderly, there is a decrease in the epidural space and cerebrospinal fluid volume.

In peripheral nerves, the distance between schwann cells decreases which increases sensitivity of the elderly to neuroaxial techniques and blockades. Decreased parasympathetic and increased sympathetic tone leads to a limited compensatory increase in heart rate and blood pressure when preload rises.

Frequent anemia in the elderly is probably associated with resistance to erythropoietin and «aging» of stem cells. Decreased immunity leads to ineffective infection resistance and prevents rapid healing of wounds [12]. In older patients, the proportion of adipose tissue increases up to 40% and that of water up to 15% of the total body weight, while the muscular mass decreases, even if a constant weight is maintained. Decreased muscle mass and function and reduced mobility increase the rate of thromboembolic complications [11].

The changes in pharmacokinetics and pharmacodynamics in elderly and senile patients are also remarkable. Aging is accompanied by a decrease in plasma albumin by an average of 10–25% due to reduced protein intake and hepatic protein synthesis. Hypoalbuminemia leads to a decrease in the protein-bound fraction of medications and an increase in the concentration of the free fraction, which alters the drug distribution and increases their pharmacological activity with increased risk of overdose and toxic reactions [13]. Minimum alveolar concentration (MAC) of inhaled anesthetics decreases approximately by 6% every decade after 40 years. For intravenous hypnotics (propofol) a 20% reduction in induction dose is required. Respiratory arrest due to low clearance of drugs in chronic renal failure is the major complication due to opioids in the elderly. Sensitivity to fentanyl increases and its activity doubles with age presumably because of sensitization of brain receptors. Pharmacodynamics of muscle relaxants does not change significantly with age. Pharmacokinetics may change toward an increase in duration of drug action due to reduced hepatic metabolism and renal function. The use of local anesthetics in elderly patients is not associated with an increased risk of adverse events, but systemic toxicity should be considered when choosing these drugs [8].

Types and Methods of Anesthesia Support for Total Knee Arthroplasty

Both general anesthesia and regional methods are used for anesthesia during total knee arthroplasty (TKA). The regional anaesthesia is considered the method of choice [14, 15] associated with less intra- and postoperative stress and more reliable block of nociceptive afferent signaling. «Standard» general anesthesia often does not provide adequate protection of the central nervous system from perioperative stress due to the complexity of selecting a timely adequate dose of intraoperative opioid analgesics [15]. Therefore, anesthesiologists can use combined anesthesia, which is especially relevant in elderly patients, adding various components of regional methods to ensure sufficient anesthesia and minimize the risk of complications.

General Anesthesia

Currently, second- and third-generation halogenated anesthetics (isoflurane, sevoflurane, desflurane) are most commonly used for anesthetic support of surgical interventions. They all have an identical mechanism of action, which consists in enhancing the inhibitory effect of GABA by interaction with GABA receptors of the central nervous system [16, 17].

The advantages of general anesthesia based on halogenated anesthetics include their availability, low cost and compatibility with a wide range of anesthesia machines. Moreover, additional training of physicians switching to these anesthetics is not required. The distinct bronchodilator effect, sufficient myorelaxant properties, the effect of anesthetic preconditioning of the myocardium typical of this group of anesthetics can also be emphasized [18–20].

At the same time, these anesthetics may cause side effects and complications in older patients. Thus, isoflurane, a second-generation inhalation anesthetic, may irritate bronchial mucosa, increase bronchial gland secretion and mucus accumulation in the airways, which subsequently may lead to bronchial obturation and lung atelectasis [16]. Halogenated anesthetics in high concentration (more than 1 MAC) reduce peripheral vascular resistance, left and right ventricular contractility, left ventricular diastolic function, and baroreceptor-mediated reflex control of blood pressure [21], which may affect patients with limited cardiovascular functional capacities. Halogenated anesthetics can also act as triggers of malignant hyperthermia [22–24].

The perioperative use of narcotic analgesics as a component of general anesthesia in elderly patients increases the risk of cognitive impairment with possible delirium [25, 26]. This requires additional sedation, hampers early activation, and can certainly lead to an increased risk of failure of cardiovascular compensatory capacity, decompensation of comorbidities, and various complications, including infectious ones, and can result in a prolonged hospital stay.

Currently, tracheal intubation is by far the most common, efficient and reliable technique for airway maintenance. However, this method has several limitations including invasive character and possible traumatic effect (direct laryngoscopy, tracheal intubation, cuff overblowing with the risk of tracheal wall damage, injury to esophagus and bronchi), hyperdynamic response of blood circulation, laryngeal mucosal edema, laryngospasm, and requirements for muscle relaxants and narcotic analgesics [27].

In recent decades, the use of laryngeal masks (supraglottic airway devices) as an alternative to tracheal intubation has become widespread worldwide. First described by British anesthesiologist Archibald Brain in 1983, the laryngeal mask quickly gained popularity worldwide [28]. And already in 1992, 59% of all general anesthesias in Great Britain were performed using this supraglottic airway [29]. It is placed non invasively and lacks negative aspects associated with tracheal intubation [30, 31].

The use of laryngeal mask has practically no adverse effect on pharyngeal and laryngeal structures thereby reducing the risk of their injury. Mask placement in laryngeopharynx causes minimal reflexogenic and hemodynamic changes and is better tolerated by patients after surgical intervention [32]. This technique also has its limitations. In particular, the laryngeal mask should not stay in oropharynx more than 4 hours, it is relatively contraindicated in patients weighing over 100 kg and fully contraindicated in those in prone position. Complications include oral mucosal injury, hematoma, rarely arytenoid cartilage dislocation or laryngeal and recurrent laryngeal nerve paralysis. A laryngeal mask is also not recommended if the patient is not deeply sedated [28].

Neuraxial Blocks

Spinal anesthesia is one of the modern methods widely used in knee arthroplasty surgeries. The main risks of spinal anesthesia are severe hypotension, bradycardia due to severe sympathetic block [33, 34] and, as a consequence, possible cardiovascular deterioration. Usually, the period of anesthesia when using this method lasts no more than 11–13 hours, and is realized by using adjuvants (clonidine, morphine), among others. The use of adjuvant drugs can lead to such side effects as respiratory depression, nausea, vomiting, profound sedation, urinary retention, skin itching, and hypotension [35]. Despite all the positive effects and cost-effectiveness, the role of this method for postoperative pain management is questionable due to the possible negative effects of adjuvants [15].

Epidural analgesia could be considered rather effective method of anesthesia during knee arthroplasty surgery. This method, as well as the perioperative use of opioid analgesics, provides sufficient analgesia and its efficiency is not inferior to that of peripheral nerve blocks [35]. Some evidence suggests that the use of regional anesthesia techniques in older patients reduces the risk of delirium [36]. The most serious disadvantages of neuraxial blocks include infectious complications at the injection site and post-dural puncture headache [37]. In modern anesthesiology, epidural analgesia should be used on strict indications with the mandatory assessment of risk/benefit ratio [38].

Peripheral Nerve Block

Peripheral nerve block is an effective method with a high safety profile. It effectively relieves acute postoperative pain, according to several studies, prevents its persistence [39], as well as reduces the use of opioid analgesics, and, as a result, increases patient satisfaction with the quality of treatment [40]. There is an opinion that peripheral nerve blocks of the lower extremities can promote motor neuropathy of the quadriceps femoris muscle [41], which can slow down motor function recovery and thus increase the risk of patient falls [42]. L.Turbitt et al. list the factors increasing the risk of inpatient falls which include male sex, water and electrolyte disorders, obesity, delirium, old age and anemia. The researchers found no significant relationship between the incidence of falls and the method of analgesia: with general anesthesia, the risk of falls was 1.6%, while with peripheral nerve blocks, it was 1.3% [43].

Systemic toxicity of local anesthetics in various regional blocks was also reported [35]. All currently used local anesthetics are effectively employed for infiltration anesthesia, but the anesthetics with the longest duration of action and the least toxicity are still preferred. Levobupivacaine and ropivacaine have a clinical profile similar to bupivacaine, however, these three drugs have different strength of analgesic effect: bupivacaine > levobupivacaine > ropivacaine [14]. Lower toxicity suggests the use of levobuvicaine and ropivacaine in sutuations where the risk associated with unintentional intravascular injection or overdose is high, e.g., in peripheral nerve blocks. With its low toxicity, ropivacaine can be considered the anesthetic of choice for regional blocks of the lower extremities, given its adequate analgesic effect and duration of action.

Despite uncommon side effects, regional blocks have a high safety profile and minimally affect hemodynamic parameters in elderly and senile patients, which is critical for patients with low functional capacities.

Ultrasound Navigation in Peripheral Nerve Blocks

The long-term experience of performing peripheral nerve blocks under ultrasound (US) control has conclusively demonstrated their usefulness.

According to experts, there is no significant advantage of ultrasound navigation over neurostimulation [38] when performing peripheral blocks. Important advantages of ultrasound navigation include visualization of the needle tip and surrounding tissues, as well as the visual assessment of anesthetic distribution, which ultimately results in shorter procedure time [44], lower volume of injected anesthetic, and, consequently, lower risk of systemic toxicity. The risk of postoperative neuropathy is believed to decrease when using ultrasound control due to the possibility of nerve visualization and prevention perineural injection of anesthetic, which cannot be completely avoided when using neurostimulation due to the specific character of the nerve motor response [45]. The main limitations of ultrasound navigation are the cost of ultrasound devices and the need for additional training of physicians.

Thus, there is no ideal anesthesia techniques with all of them having obvious pros and cons. The choice of anesthesia technique is particularly difficult in elderly patients with comorbidities. In knee arthroplasty in this group of patients, anesthesia should meet such requirements as sufficient analgesic effect with minimal use of opioid analgesics, cardio- and neuroprotective properties with no significant effect on hemodynamics. These beneficial effects allow to avoid postoperative decompensation of vital organs.

A combination of peripheral nerve conduction block of the lower extremity and xenon-based general anesthesia with a laryngeal mask can satisfy these requirements. Moreover, the use of xenon alone anesthesia has certain limitations reported in the literature.

Xenon

Xenon (Xe) is called a «noble» gas because it is present in the atmosphere in very small concentration of as low as 0.0000087%. Xenon was first discovered by the English scientists W. Ramsay and M. Travers in 1898. They performed slow evaporation of liquid air and spectroscopic examination of its most volatile fractions. This gas is used in the manufacturing of lasers, filling the incandescent light bulbs, passivation of metals, X-ray tubes, in the space industry, as well as in medicine for sedation and anesthesia [46, 47]. For about 70 years xenon has been used in anesthesiology [48]. During this time, a large body of clinical data has been accumulated demonstrating its safety and efficacy [49], absence of teratogenic and toxic properties [50]. Various studies have shown numerous benefits of xenon when compared with inhaled anesthetics of other classes. Xenon has the lowest blood/gas solubility ratio (0.14) which is responsible for a faster onset and termination of action [51]. The gas does not depress cardiovascular psrsmeters maintaining hemodynamic stability [52] and possesses neuro- and organoprotective properties which is very important in elderly patients with comorbidities [53, 54]. It has adequate analgesic properties [55].

Moreover, xenon is characterized by high-level environmental safety and lacks ozone-depleting properties. Wide use of xenon anesthesia in clinical practice is impeded by its high cost and the need for a special closed circuit of anesthesiological and ventilatory equipment, as well as additional staff training for working with xenon. Recycling techniques, improved technology of xenon production and use, avoidance of open circuit inhalation could reduce the cost of anesthesia and provide a rationale for its broader administration [56].

Mechanisms of Anesthetic Action of Xenon

Mechanisms of action and «targets» of xenon remain unclear. Some researchers believe that xenon acts through inhibition of N-methyl-D-aspartate (NMDA) receptors). N.Franks et al. demonstrated 60% inhibition of NMDA-receptor activity on exposure to xenon at concentration of up to 80% [57]. Xenon differs from other drugs blocking NMDA receptors in inhibiting 5NT3-receptors responsible for postoperative nausea and vomiting, as well as central and peripheral nociception [58].

Anesthesiological Aspects of Xenon Use

The minimum alveolar concentration of xenon ranges from 63 to 71% [59]. For this reason, its use for monoanesthesia is hazardous due to the dangerous reduction of inhaled oxygen fraction below 30% for reaching the 1 MAC level, which can be especially harmful in patients with limited functional capacities. The awakening MAC of xenon is 33% (0.46 of 1 MAC), which is less than that of nitrous oxide (0.61 MAC) but greater than that of the second- and third-generation halogenated anesthetics sevoflurane and isoflurane (0.35 MAC). Prolonged inhalation of xenon mixture had no effect on the ultimate prolongation of awakening time [60]. Faster recovery of consciousness in patients receiving xenon versus propofol anesthesia was clearly demonstrated (3 min 11 sec vs. 25 min 23 sec), as well as faster awakening and recovery period in patients older than 60 years (260 sec vs. 590 sec) [61]. In elderly and senile patients, awakening after anesthesia with xenon, compared with desflurane, was also faster, with complete cognitive restoration within half an hour after the end of anesthesia [62].

V. Likhvantsev describes xenon performance as follows: «In some cases, for example, for gastric resection, its use as a single agent is enough, while in other cases it is not sufficient for a routine hernioplasty» [63]. In the clinical setting, an increased frequency of postoperative nausea and vomiting (PONV) in patients after anesthesia with xenon mixture vs propofol anesthesia has been reported [58]. Frequency of postoperative nausea and vomiting was 66.2% in xenon anesthesia group and 26.8% in propofol group, according to M. Coburn et al. data [64]. Pharmacoeconomic burden of xenon anesthesia varies from about $60 per 1 liter of xenon in USA to 30$ and higher in European countries [65]. Possible prospects of cost reduction are still remote. According to our own data, the average consumption of xenon gas in cost-effective automatic mode of Taem (France) apparatus is about 20 liters during a 3-hour long anesthesia. Moreover, not all current anesthesia machines are able to operate on a closed circuit, as required for economic consumption of xenon and its further recycling.

Effect of Xenon Znesthesia on the Cardiovascular System

According to literature and clinical data, xenon inhalation anesthesia is characterized by stablility of hemodynamic parameters and lack of cardiovascular adverse effects in the perioperative period [66-70]. The repeatedly recorded and clinically observed decrease in heart rate during xenon anesthesia can be explained by its impact on the sympathetic/vagal balance [71]. A 2018 meta-analysis, which included 13 studies, compared xenon anesthesia with propofol-based total intravenous anesthesia. Xenon anesthesia was shown to provide higher mean arterial pressure (MAP) values in the intraoperative period (87.5±14.06 mmHg with xenon vs 80.3±14.53 mmHg propofol; P<0.01), lower heart rate (56.75±10.78 beats per minute with xenon, 65.87±12.37 beats per minute with propofol; P<0.01) [59]. More severe decrease of heart rate in xenon anesthesia in comparison with propofol has been described by J. Höcker et al, the frequency of vasopressor drugs did not differ between the groups [72]. The authors, who based their studies on stability of epinephrine and cortisol levels in plasma, believe that hemodynamic stability during xenon anesthesia is due to sympathetic activation in response to surgical stress [73]. A. Belov et al. have shown that hemodynamic parameters were more stable throughout the surgery in xenon group compared with nitrous oxide group during endoscopic operations in gynecology [74]. Animal studies have demonstrated cardioprotective properties of preconditioning with xenon during a 60-minute occlusion of anterior interventricular artery in pigs [75]. In other experiments, no significant differences were observed between patients who had inhalation anaesthesia with 50% xenon mixture, those who had 50% nitrous oxide and 95% oxygen anesthesia. The coronary perfusion pressure was 44±1 mmHg in the 95% O_2 group, 40±1 mmHg in the 50% Xe group, and 38±2 mmHg in the 50% N_2O group, left ventricular perfusion pressure was 102±3 mmHg in the 95% O_2 group, 66±3 mmHg in the 50% Xe group, and 73±4 mmHg in the 50% N_2O group. The decrease in these parameters when using anesthetics was mainly due to overall reduction of oxygen delivery (DO_2) associated with the reduction of its fraction in the breathing mixture (it was 130±4 ml/min with 95% O_2 and 66±2 ml/min with 45% O_2) [76]. In an experiment of 60 male rats subjected to 60-minute coronary artery occlusion and then 120-minute reperfusion, the xenon group showed a smaller reduction in cardiac output (62±9%) than the isoflurane group (49±7%) after 4 weeks [77]. Experiments with pigs administered with 70% xenon have demonstrated cardiac output reduction by 30% on average and increase in pulmonary artery compliance by 60%, which resulted in right ventricular ejection fraction reduction by 25% [78]. Another study has revealed that 20% xenon in combination with hypothermia down to 34°C, reduced infarct size in rats who underwent 25-min coronary artery occlusion followed by 120-min reperfusion [79]. In an experiment performed on rabbits with left ventricular dysfunction (after coronary artery ligation), inhalation of 50% xenon neither reduced myocardial function nor caused significant ECG changes [80].

Neuroprotective Effects of Xenon

The neuroprotective effects of xenon have been clearly demonstrated [81].

The damaging effects on the brain in hemorrhagic or ischemic stroke, traumatic brain injury, and cardiac arrest have a similar pathogenesis, realized through the mechanism of excitotoxicity directly involving the NMDA. The mechanisms determining neuronal damage are multifactorial, but excitotoxicity is the major one. NMDA-receptor activity is important for many neurological functions, which require synaptic compliance, mood control, memory formation, motivation, progression of brain activity and neuronal survival [82–85]. At the same time, excessive activation of NMDA receptors under stress conditions can lead to neuronal death, a process described as excitotoxicity [83, 86]. It occurs when neurons are exposed to high doses of glutamate, which leads to increased calcium influx through calcium channels and activates an excessively high inflow of extracellular calcium [87, 88]. Excitotoxicity is the underlying mechanism of many neurodegenerative disorders, both acute (brain injury, stroke) and chronic (Parkinson's disease, Alzheimer's disease). After obtaining data on the mechanism of action of xenon (NMDA-receptor inhibition), several papers have been published on the protective effects of xenon on experimental neuronal cell cultures exposed to glutamate or oxygen-glucose deprivation [89, 90].

Xenon can realize neuroprotection by acting on bipolar potassium channels (TREK-1) which provide an ionic current reducing neuronal excitability and protecting neurons from damaging effects (a similar mechanism has been reported for the preconditioning effect of sevoflurane [58]).

Currently, there is an ongoing discussion about the importance of adenosine triphosphate (ATP)-sensitive potassium channels of the cell membrane in the mechanism of neuroprotective effects of xenon. In vitro studies have shown that in neuronal culture xenon exhibited protective effects due to activation of ATP-sensitive potassium channels in the outer cell membrane [91].

In traumatic brain injury, according to experimental data, prolonged inhalation of xenon (at least for 3 hours) improved vestibulomotor function and memory in the late period of injury. The neuroprotective effects of xenon were shown to be associated with a decrease in neuroinflammation in the brain areas that play a role in the implementation of associative memory. Xenon showed its neuroprotective properties up to 20 months after the injury episode [92].

A review paper reported that inhalation of xenon after a transient ischemic attack in rats resulted in reduction of the infarct volume and neurological deficit within 7 days after the ischemic episode [53].

R. Laitio et al. have shown that inhalation of 40% xenon combined with hypothermia during 24 hours after an out-of-hospital cardiac arrest leads to less brain damage in comparison with hypothermia alone. This was further confirmed by magnetic resonance imaging. Half-year mortality was 27% in the xenon group with hypothermia and 35% in the hypothermia alone group. The difference between the groups, though, was not significant ($p=0.053$) due to insufficient sample size (110 patients). Similar results were obtained in other experiments [93, 94].

The Problem of Intraoperative Awareness and Assessment of the Depth of Hypnosis with Xenon

Despite the above-mentioned advantages of xenon for anesthesia in high-risk patients, there are also several challenges in its use in anesthesiology. In particular, this refers to objective instrumental assessment of the depth of hypnosis, which is directly related to the issue of intraoperative awareness.

The American Society of Anesthesiologists (ASA) has recognized the importance of studying intraoperative awareness episodes and in March 2007 opened a registry to collect detailed and current information to increase knowledge about intraoperative awareness and its risk factors. Unintended awareness during operation can occur in patients for a variety of reasons. After such episodes, patients may develop postoperative psychological disorders of varying severity [95]. Sleep disturbances are observed in 19% of patients, nightmares in 21%, fear of anesthesia in 20% of patients, and persistent anxiety in 17%. Delayed psychological signs that can lead to posttraumatic stress disorder were first described by Meyer and Blacher in 1961. According to Samuelsson et al, these symptoms develop in 33% of patients who have had an episode of intraoperative awareness [96]. However, the rate of intraoperative awareness episodes has decreased from 1.2% and 0.8% in the 1960s and 1970s to the current rate of 0.1–0.2% as anesthesia techniques have improved [97, 98].

To prevent intraoperative awareness, including in operations with inhalation anesthetic concentration below 0.7 MAC, preoperative low-dose midazolam, subanesthetic doses of ketamine, or preventive myorelaxant antidotes on hypnotic discontinuation at the end of surgery or a combination of general inhaled anesthesia with regional anesthesia should be considered [99].

The use of hypnotic depth monitoring is intended to reduce the frequency of intraoperative awareness episodes and can also be useful for preventing excessive sedation, which may lead to increased risk of cognitive decompensation, especially in elderly and senile patients [100, 101]. Researchers are still seeking ways to effectively assess the depth of xenon hypnosis, but the issue remains poorly understood.

The most common and generally accepted method for objective instrumental assessment of hypnotic depth is bispectral index (BIS) monitoring. Several studies report relatively low informative value of BIS during xenon anesthesia [102]. The BIS algorithm is based on the electroencephalogram (EEG) database validated on the drugs interacting with GABA receptors (propofol), and this method is completely inappropriate for anesthetics with NMDA-blocking properties (ketamine, xenon) [103, 59]. The literature data on relationship between BIS values and clinical presentation are inconsistent [104]. J. Höcker et al. made conclusions about the possible comparability of BIS monitoring parameters during anesthesia with xenon mixture and propofol anesthesia in elderly patients, but at the same time the authors were not entirely confident in their findings [105].

In the early 2000s, a digital method of spectral assessment of EEG based on entropy was introduced [106]. In their studies evaluating BIS values and entropy changes during propofol and xenon anesthesia, Höcker J. et al. showed that entropy level was significantly lower than the similar BIS index level in xenon anesthesia group, while in propofol group the data were comparable [72]. Laitio R. et al. in their study reported that BIS and entropy monitoring data correlated with the clinical presentation in the main phase of surgery during deep anesthesias but were not consistent with the clinical picture during the induction phase and at the end of anesthesia, during awakening, when xenon was used. Thus, the use of BIS and entropy monitoring techniques during xenon anesthesia appears to be only an adjunctive method and should not downplay the clinical presentation assessment [107].

The method based on the measurement of auditory evoked potentials (AEPs) can be used in assessing the depth of hypnosis and during the awakening phase [108]. This monitoring technique uses the mechanism of measuring the attenuation of evoked auditory potentials during surgical treatment under the impact of drugs used during anesthesia. An increase in latency and a decrease in AEP peaks corresponds to an increase in anesthetic concentration and directly correlates with the level of sedation of the patient. In a randomized study including 60 patients anesthetized with xenon, sevoflurane, and isoflurane in combination with epidural anesthesia, Goto T. et al. demonstrated that AEPs significantly correlated with clinical picture of awakening and recovery after anesthesia [109]. The technique of AEP is not commonly used in clinical practice, and no data on inconsistency of its results with the clinical presentation when xenon is used have been found.

EEG monitoring provides more complete and objective information about the depth of hypnosis compared with processed EEG parameters (BIS, EAP, entropy) even after the use of muscle relaxants, hypnotics or narcotic analgesics [110]. When the patient is awake, the raw EEG usually has predominant beta activity (20 to 30 Hz), the awake patient with eyes closed has sequential alpha rhythm waves (8–14 Hz) with an increase in slow-wave Theta (4–8 Hz) and Delta rhythms (0.5–3 Hz) noted during the transition from the initial to deep sleep stage [111]. The raw EEG waveform during general anesthesia varies depending on the classes and combinations of anesthetics administered and appears to be more valuable when specially trained specialists are available in the operating room. There is convincing evidence showing the feasibility of assessing the depth of hypnosis based on EEG changes during anesthesia using the validated Kugler scale, in which the stages of sedation depth are divided into 16 levels depending on the predominance of EEG rhythm type at the time of signal recording [112]. In clinical practice, this is difficult to implement due to the need to decode the EEG signals obtained during surgery in the operating room.

The character of EEG changes during xenon anesthesia was discussed in selected papers, which can be used to assess the depth of hypnosis. The electroencephalogram changes are identical during anesthesia with xenon mixture and nitrous oxide. A decrease in the activity of alpha rhythm and increase in theta and delta waves are observed as the concentration of gas in the mixture increases [107]. V. Potievskaya et al. evaluated EEG changes during inhalation of xenon-oxygen mixture and pointed out that with increasing concentration of xenon-oxygen mixture on inhalation, a clinically evident increase in the depth of sedation (up to –2 points on the RASS scale) is seen, along with the replacement of the fast-wave alpha rhythm by slow-wave theta and delta waves and subsequent gradual recovery to their original ratios with decreasing xenon concentration in the inhaled mixture [113].

The literature data on EEG changes corresponding to xenon anesthesia stages, comparable with the validated Kugler scale, cases of intraoperative awakening associated with xenon anesthesia, as well as retrograde amnesia effect when using xenon were not found. This issue requires an additional research.

Conclusion

The choice of anesthetic method for knee arthroplasty in elderly and senile patients requires assessment of the risks of decompensation of cardiovascular and cognitive disorders. None of the known methods of anesthesia is ideal in terms of safety. The use of xenon as the main anesthetic seems promising with regard to its cardioprotective and neuroprotective properties. However, its use is limited by relatively high cost, and therefore, the search for optimal (reduced compared with the recommended) concentration on inhalation may expand its administration in elderly and senile patients. However, lower xenon concentrations are associated with intraoperative awareness and the need for its combination with narcotic analgesics or amnestic drugs. In addition, the effect of retrograde amnesia of xenon to protect the patient from intraoperative stress of unintended intraoperative awareness has not been studied, and routine methods of hypnotic depth monitoring when using xenon often produce results that do not correlate with the clinical presentation. Therefore, further research is needed to examine the effects of xenon on retrograde amnesia and to find optimal methods for assessing the depth of hypnosis on xenon to safely reduce its concentration on inhalation.

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