Multimodal Anesthesia Using Xenon and Transcutaneous Electrical Nerve Stimulation During Dental Implantation

Igor Alexandrovich Shugaylov[1], Oleg Nikolaevich Moskovets[2], Dmitry Konstantinovich Yudin[3], Igor Anatolyevich Zinovjev[4]

[1]*Academy of Innovative Dentistry, Moscow, Russia*

[2]*Moscow State University of Medicine and Dentistry named after A.I. Evdokimov, Moscow, Russia*

[3]*Moscow Cancer Research Institute named after P.A. Herzen, Moscow, Russia*

[4]*Moscow State University of Medicine and Dentistry named after A.I. Evdokimov, Moscow, Russia*

[1] *shugaylov.i.a@mail.ru*

Abstract *— The use of xenon in medicine has great potential for increasing the efficiency and safety of general medicine and surgical service. Over the past decades, the development of methods for the use of xenon has significantly intensified, however, work in this direction is mainly limited to experimental studies on animals. In this research, the authors studied the effect of conscious sedation by preliminary inhalation using 30/70 xenon-oxygen mix during dental implantation on the amount of pain, indicators of the psychoemotional state, central hemodynamics, the amount of pain and tissue swelling in the postoperative period, the ratio of the sympathetic tonus and parasympathetic tonus, and saturation of peripheral blood with oxygen at the stages of operation. Additionally, transcutaneous electrical nerve stimulation and local anesthesia, which use mechanisms of an antinociceptive effect that differ from that of xenon, were used to increase the pain-alleviating effect. A group of patients that received only local anesthesia was used for comparison. The use of multimodal anesthesia significantly reduced the anxiety and depression, stabilized the arterial pressure and reduced the cardiac rate, increased the parasympathetic tonus and oxygen saturation, reduced the amount of pain at the stages of operation and in the postoperative period, and reduced edema on the third day after the operation. Reduced soreness at all stages of the operation allowed significantly reducing the consumption of local anesthetic and using a less traumatic technique for local anesthesia. Patients showed no negative psychoemotional reactions and somatic complications during surgery; there were no complications during the period of adaptation and integration of implants. It was shown that pronounced parasympathicotonia developed after inhalation of xenon-oxygen mix, which can cause the development of a side effect of xenon – postoperative nausea and vomiting. The additional use of transcutaneous electrical nerve stimulation reduced the parasympathetic tonus, potentiated the pain-alleviating effect and did not have a significant effect on the psychotropic effect of xenon. The proposed method of short-period preliminary inhalation of xenon-oxygen mix provides proper anesthesia, increases the safety of the intervention and allows obtaining high clinical results for the treatment of patients with various forms of edentia.*

Keywords *— xenon, dental implantation, transcutaneous electrical nerve stimulation, adentia, psychotropic effect, antinociceptive effect, Multimodal anesthesia.*

I. INTRODUCTION

Stomatological implantological methods are currently widely used in the treatment of patients with various forms of edentia [1]. Dental implantation, like most oral surgeries, has a moderate degree of invasiveness. However, anesthetic management for this operation has several features, which include the following:

1. The need for effective anesthesia due to the high degree of innervation of the tissues of the maxillofacilal area,
2. A higher risk of psychoemotional reactions and somatic complications, since patients seeking this type of treatment have a history of several concomitant somatic diseases, as most of them are elderly people

What is more, the postoperative period is very important: during it, pain syndrome and edema should be reduced to prevent early postoperative complications that impede osseointegration.

Local anesthesia (LA) traditionally and widely used in the treatment of dental diseases does not satisfy all these requirements. There is an obvious need for the development of anesthesia methods that would ensure effective intraoperative and postoperative analgesia, psychovegetative protection, and prevention of complications during the adaptation and osseointegration of the implants.

The use of xenon has undoubted potential for the development of methods of pain relief. Numerous studies conducted over the past two decades indicate

that inhalation of xenon-oxygen mix in therapeutic doses provides analgesic, psychosedative, vegetative stabilizing, neuroprotective, organoprotective, anti-inflammatory, and immunoprotective effects [2-8]. However, the degree of analgesia that can be obtained using therapeutic doses of xenon is insufficient.

To enhance the analgesic endpoint of inhalation of xenon-oxygen mix, various combinations with other analgesic methods and tools are used: inhalation, endovenous injections, LA (epidural analgesia), and others. In our earlier research, we studied the features of the transcutaneous electrical nerve stimulation (TENS) in experimental studies [9] and the surgical treatment of dental diseases [10]. The optimal parameters of electrical stimulation for its use in the maxillofacial area and the features of developing antinociceptive effects were determined. In experimental studies, three types of antinociceptive effects were identified depending on the parameters of electrical stimulation:

– The first type of effect was characterized by rapid development (50 ms), short duration of effect (less than 150 ms), and the lowest degree of reduction of nociceptive reactions. Electrophysiological analysis of the mechanisms of this effect showed that they were similar to the "Gate control" described by Melzak and Wall in 1965.

– The second type of effect, in which the inhibition of nociceptive reactions was not blocked by naloxone, was characterized by a slow development (10 min), a relatively short duration of effect (40-50 min), and a low degree of reduction of nociceptive reactions. This effect, according to the data, can be mediated by activation of the mechanisms of the monoaminergic antinociceptive system.

– The third type of effect, in which the inhibition of nociceptive reactions was blocked by the administration of naloxone, was characterized by slow development (15 minutes), the longest duration of effect (more than two hours), and the greatest degree of reduction of nociceptive reactions. According to our data, this effect can be mediated by the activation of the mechanisms of the opioidergic antinociceptive system.

In clinical studies, it was found that the analgesic effects of the use of TENS in same-day dental procedures were comparable to the use of 1% novocaine solution LA. Additionally, they were comparable with the use of piritramidum at a dosage of 7.5-15 mg and significantly exceeded the effects of trimeperidine at a dosage of 10-20 mg, based on the data from extensive operations in the hospital. It was also found that TENS:

- does not cause toxic effect,
- is unable to cause an allergic reaction,
- has a controlled time of effect,
- is not invasive,
- does not have absolute contraindications,
- is easy to use.

The aim of the study was a comparative assessment of the effectiveness and adequacy of multimodal anesthesia using inhalation of xenon-oxygen mix, TENS and LA during dental implantation.

Research objectives included the study of the following:

- emotional and personal characteristics and their change under the influence of anesthesia;
- dynamics of systolic, diastolic and mean arterial pressure, cardiac rate, as well as the saturation of peripheral blood with oxygen during different stages of the operation;
- amount of pain at the stages of the operation;
- dynamics of the amount of pain in the first, second and third days of the postoperative period;

the severity of edema on the third day after surgery.

II. MATERIALS AND METHODS

Studies were conducted on three groups of patients with secondary edentia during the dental implantation surgery which included the installation of Nobel Biocare and Alpha BioTec endosseous implant systems. In the first group, only LA was used for anesthetization. In the second group, a combination of preliminary inhalation of xenon-oxygen mix (Xe) and LA (Xe + LA) was used for anesthetization. In the third group, the combination of TENS, inhalation of xenon-oxygen mix and LA (TENS + Xe + LA) was used for anesthetization.

There were 20 patients in the first group (age 38-63 years), and they all completed the study. There were 20 patients in the second group (age 39-66 years), all of whom also completed the study. The number of patients in the third group was 19 people (age 37-65 years), but only 17 of them completed the study. Two patients in the third group did not pass the examination in the postoperative period. The distribution of patients in groups by gender, age, and physical condition is presented in Table 1.

Table 1. The distribution of patients in groups by gender, age and physical condition

A. Groups	Parameters	Age (years)			
		30-39	40-49	50-59	60-69
B. **1** ***C.*** LA	number (male/female)	2 (1/1)	5 (3/2)	8 (4/4)	5 (2/3)
	physical condition (ASA)	ASA I	ASA I-II	ASA I-II	ASA II
D. **2** ***E.*** Xe + LA	number (male/female)	1 (1/0)	4 (3/1)	9 (5/4)	6 (2/4)
	physical condition (ASA)	ASA II	ASA I-II	ASA II	ASA II
F. **3** ***G.*** TENS + Xe + LA	number (male/female)	3 (2/1)	5 (2/3)	8 (4/4)	3 (2/1)
	physical condition (ASA)	ASA I	ASA I-II	ASA I-II	ASA II

Designations: LA – local anesthesia, Xe – inhalation of xenon-oxygen mix, TENS – transcutaneous electrical nerve stimulation.

4% solution of articaine with epinephrine at a concentration of 1:200,000 was used for LA. The introduction of the local anesthetic was carried out both by infiltration and conduction methods. Application anesthesia was not used during the injection for two reasons. First, the application of anesthetics is accompanied by contamination of the sterile surgical area. Second, we used the measurement of the painfulness of the injection (using visual analogue scale – VAS) for the subsequent determination of the effect of the studied methods of pain relief.

Inhalation of xenon-oxygen mix at the concentration of 30/70 lasted for three minutes and was conducted by a dentist using the KTK-01 device (Russia) based on permits for the use of medical technologies [11, 12]. Methodical guidelines for the use of xenon [13] were used to determine the criteria for the inclusion of patients in the study and the use of inhalation.

The xenon-oxygen mix inhalation procedure consisted of several stages. Initially, the dentist had a conversation with the patient to familiarize them with the procedure and explain its goals and the expected medicinal effect. The patient received information on the subjective sensations that they might experience during inhalation (peripheral paresthesias, hypoalgesia, numb feeling, heaviness in the legs at the beginning of the procedure, and a feeling of lightness at the end of the procedure). An inhalation mask was selected. The procedure began with flushing of the ventilator circuit with 100% oxygen in a semi-open mode. Then the ventilator circuit was switched to the closed mode and one or two liters of xenon were supplied. To ensure that the patient had adequate respiratory volume (three liters), one liter of oxygen was also added to the circuit until the respiratory bag was filled. Upon completion of the preparatory procedures, a mask was given to the patient during exhalation and the procedure of xenon-oxygen gas mix inhalation was started. Due to the intensive absorption of xenon and oxygen by the body during the first minutes of inhalation, the volume of the gas mix in the bag was significantly reduced. Because of that, the additional supply of gases to maintain adequate respiratory volume and xenon concentration of 30-35% was needed. The duration of xenon exposure before performing LA was three minutes. After this, LA and surgery were performed. In some cases, a test inhalation was performed before the main procedure.

For TENS, round electrodes (d=10 mm) were used, which were placed on the skin surface at the projection of the foramen during surgeries on the lower jaw or at the projection of the infraorbital foramen during surgeries on the upper jaw. The second electrode was placed in front of the antilobium (Figure 1). Electrical nerve stimulation was performed using bipolar asymmetric current pulses with a width of 20 μs and a frequency of ten pulses per second. The intensity of electroneurostimulation was selected individually for each patient to achieve intense non-pain sensations.

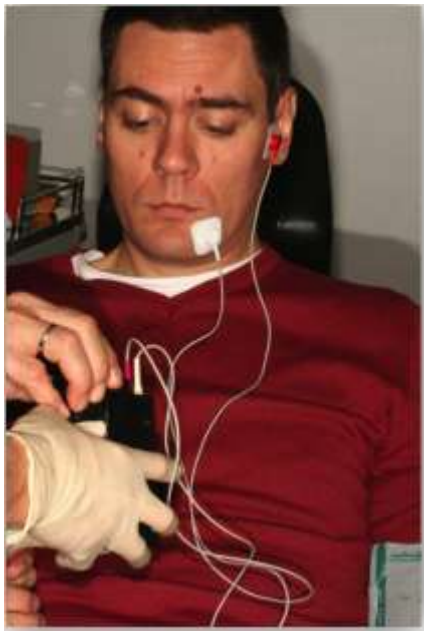


Figure 1. Application of the TENS during the surgical procedure

Clinical and physiological parameters were evaluated before analgesia, after inhalation of xenon-oxygen mix, at the stages of medical interventions (injection, incision, operation, suturing, after operation) and on the first, second, and third days after the operation.

Emotional and personal characteristics were determined using Hospital Anxiety and Depression Score (HADS) [14]. The maximum magnitude of the severity of each of the HADS indicators was 21 points. A value of more than 11 points on either of the two scales indicates "clinically apparent anxiety/depression". The total value of these two scales was used for the assessment.

Systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and peripheral blood oxygen saturation (SpO_2) were monitored during the entire operation using a finger sensor. According to central circulatory dynamics, mean arterial pressure (MAP) was calculated using the following formula:

$$MAP = DBP + (SBP - DBP)/3$$

To assess the ratio of sympathetic tonus and parasympathetic tonus, the Kerdo index (KI) was calculated using the following formula:

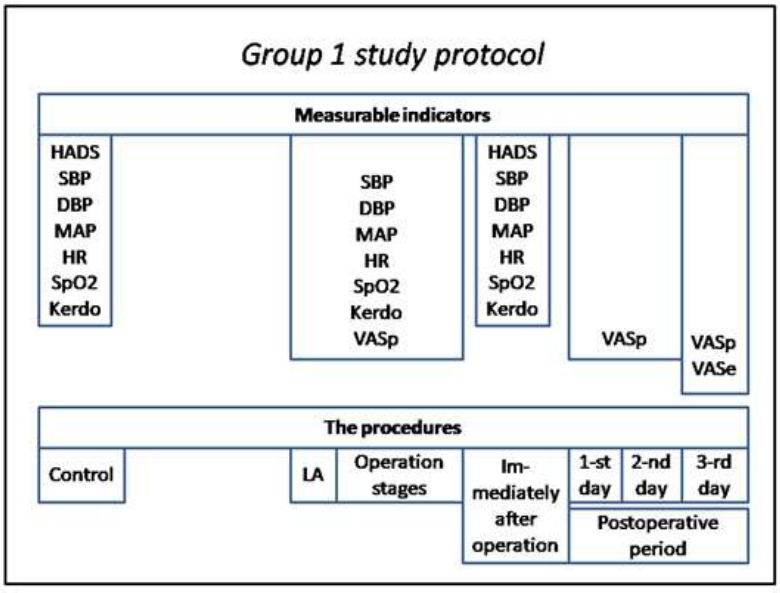
$$KI = (1 - DBP/HR) \times 100\ (\%)$$

The amount of pain during the operation and the postoperative period was evaluated on a 10-point VAS: (0 – no pain, 10 points – the most severe pain imaginable).

The severity of tissue edema was evaluated on the third day of the postoperative period according to the following VAS:

0 – no edema;
1 – edema in the flap;
2 – edema in the mucobuccal fold;
3 – visible edema of the soft tissues of the face.

Study protocols for different groups that include stages of the intervention and measurable indicators are presented in Figure 2.



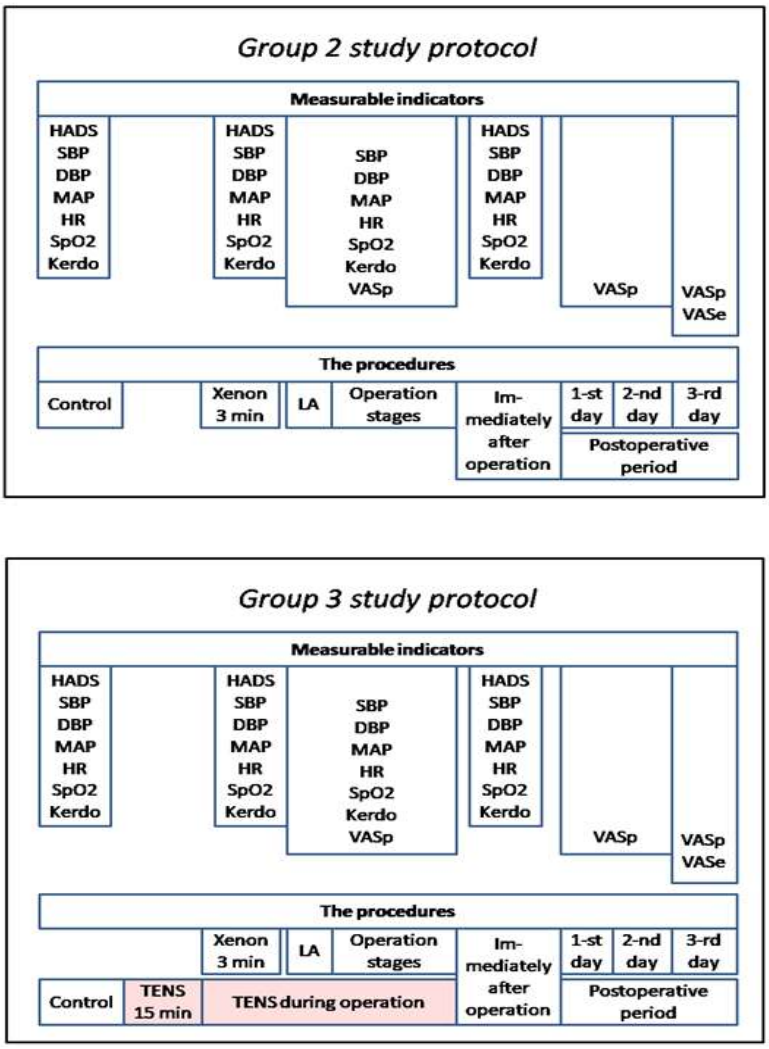


Figure 2. Research protocols for different groups that include stages of the intervention and measurable indicators. Designations: HADS – Hospital Anxiety and Depression Scale, SBP – systolic blood pressure, DSP – diastolic blood pressure, MAP – mean arterial pressure, HR – heart rate, SpO2 – blood oxygen saturation, Kerdo – Kerdo index, VASp – visual analog scale of pain, VASe – visual analog scale of edema, Xenon – xenon-oxygen mix inhalation, TENS – transcutaneous electrical nerve stimulation, LA – local anesthesia

Statistical processing of the data included the calculation of mean values and standard deviations for each group at each research stage. The statistically significant difference was determined using the Student t-test for paired comparisons or multiple comparisons with Bonferroni adjustment.

III. RESULTS AND DISCUSSION

During the surgery, from one to three dental implants were installed simultaneously, and the duration of the operation was 20-45 minutes. Xenon consumption was 1.8 liters on average in each case during the inhalation of xenon-oxygen mix. The obtained data for the studied groups and the results of its statistical processing are presented in Table 2, 3, and 4.

Table 2. Indicators of the psychophysiological state of patients during different stages of the operation in group 1 (LA)

Parameter	Stages of operation						
	Control	Xe	Injection	Incision	Operation	Suturing	After operation
HADS	10.3±3.9	-	-	-	-	-	10.3±4.1
SBP	126.5±10.7	-	128.8±14.6	127.5±11.3	126.8±11.4	126.2±11.5	125.4±10.1
DBP	79.8±8.0	-	79.8±11.4	78.1±9.2	78.7±9.5	79.8±8.4	80.1±8.1
MAP	100.4±8.8	-	101.1±12.4	99.6±9.6	99.7±9.9	100.3±9.2	100.2±8.4
HR	84.2±5.0	-	92.6±13.7	86.3±7.5	84.3±5.8	84.4±5.5	83.2±4.2
SpO_2	97.9±1.6	-	95.4±1.3	96.7±1.3	97.1±1.4	97.2±1.2	97.6±1.4
Kerdo	1.1±7.6	-	9.6±10.9	5.3±10.8	2.3±12.5	1.0±11.2	-0.7±11.4
VASp	-	-	5.7±1.3	1.5±1.1	1.4±0.9	2.5±1.1	-

Designations: HADS – Hospital Anxiety and Depression Scale, SBP – systolic blood pressure, DSP – diastolic blood pressure, MAP – mean arterial pressure, HR – heart rate, SpO_2 – blood oxygen saturation, Kerdo – Kerdo index, VASp – visual analog scale of pain, VASe – visual analog scale of edema, Xenon – xenon-oxygen mix inhalation, TENS – transcutaneous electrical nerve stimulation, LA – local anesthesia.

Table 3. Indicators of the psychophysiological state of patients during different stages of the operation in group 2 (Xe + LA)

Parameter	Stages of operation						
	Control	Xe	Injection	Incision	Operation	Suturing	After operation
HADS	10.0±3.6	5.5±2.5	-	-	-	-	5.5±2.3
SBP	130.3±12.0	137.7±11.5	133.1±12.4	127.9±9.3	125.2±9.7	124.3±9.1	125.0±10.0
DBP	86.7±7.6	90.8±6.8	87.0±4.9	82.6±4.9	81.7±4.4	81.3±3.9	81.7±3.6
MAP	101.2±8.7	107.2±7.6	102.8±6.9	98.1±5.4	96.2±5.6	95.7±4.5	96.1±5.1
HR	87.7±7.2	77.0±4.6	82.8±4.9	76.9±4.2	74.7±4.5	74.7±4.1	74.7±4.2
SpO_2	96.9±1.8	99.9±0.4	99.7±0.6	99.1±0.9	99.2±0.8	99.1±0.5	98.8±1.0
Kerdo	0.6±10.8	-18.2±8.9	-5.3±7.5	-7.7±7.7	-9.6±7.7	-9.1±9.1	-9.7±7.4
VASp	-	-	2.2±0.7	0.8±0.5	0.8±0.6	1.4±0.6	-

Designations: HADS – Hospital Anxiety and Depression scale, SBP – systolic blood pressure, DSP – diastolic blood pressure, MAP – mean arterial pressure, HR – heart rate, SpO_2 – blood oxygen saturation, Kerdo – Kerdo index, VASp – visual analog scale of pain, VASe – visual analog scale of edema, Xenon – xenon-oxygen mix inhalation, TENS – transcutaneous electrical nerve stimulation, LA – local anesthesia.

Table 4. Indicators of the psychophysiological state of patients in different stages of the operation in group 3 (TENS + Xe + LA)

Parameter	Stages of operation						
	Control	Xe	Injection	Incision	Operation	Suturing	After operation
HADS	11.7±3.0	6.5±2.8	-	-	-	-	6.3±2.3
SBP	129.3±12.2	137.4±11.1	130.2±11.1	129.5±10.4	127.3±10.2	124.3±12.1	126.9±10.5
DBP	86.7±9.4	92.9±6.8	89.6±9.3	86.2±6.5	84.8±7.1	82.7±7.9	84.4±7.4

MAP	100.9±9.5	107.8±7.4	103.1±8.6	100.6±6.6	99.0±6.9	96.5±8.5	98.6±7.4
HR	86.4±6.6	79.3±4.8	82.3±5.1	78.1±5.0	78.4±4.5	77.9±4.5	79.6±4.7
SpO_2	97.1±1.3	99.4±0.8	99.4±0.6	98.6±1.3	98.8±0.8	98.4±0.8	98.4±1.0
Kerdo	-0.5±8.1	-17.4±7.3	-7.6±9.8	-10.7±9.3	-8.1±8.2	-7.4±7.1	-6.1±7.3
VASp	-	-	1.0±0.0	0.4±0.5	0.3±0.5	0.7±0.5	-

Designations: HADS – Hospital Anxiety and Depression scale, SBP – systolic blood pressure, DSP – diastolic blood pressure, MAP – mean arterial pressure, HR – heart rate, SpO_2 – blood oxygen saturation, Kerdo – Kerdo index, VASp – visual analog scale of pain, VASe – visual analog scale of edema, Xenon – xenon-oxygen mix inhalation, TENS – transcutaneous electrical nerve stimulation, LA – local anesthesia.

Before anesthesia, HADS values were 5-18 points (10.3 ± 3.9 on average) in the first group (LA), 2-17 points (10.0 ± 3.6 on average) in the second group (Xe + LA), and 6-16 points (11.7 ± 3.0 on average) in the third group (TENS + Xe + MA), which indicates the absence of statistically significant differences between the groups ($p > 0.50$). After inhalation of xenon-oxygen mix (stage Xe), HADS values statistically significantly decreased by 1.9 ± 0.4 times ($p < 0.001$) in the second group (Xe + LA) and 2.0 ± 0.7 times ($p < 0.001$) in third group (TENS + Xe + LA), compared to the initial values. Before inhalation, HADS values were 11 points or higher in nine of 20 patients in group 2 (Xe + LA) and 13 of 19 patients in group 3 (TENS + Xe + MA). After inhalation, HADS values were 11 points or higher in only one patient in each group. Clinically, the development of a state of sedation, relaxation, and drowsiness was observed in patients. Sufficient level of sedation was achieved on the third minute of inhalation. The mask was removed and LA was administered followed by dental treatment.

After completion of the surgery, HADS values in the first group (LA) did not significantly change statistically compared to the initial values and the average was 10.3 ± 4.1 ($p > 0.500$). In groups 2 and 3, HADS values (that decreased after inhalation of xenon-oxygen mix) remained practically unchanged, which indicates the persistence of the psychotropic effect during the entire operation. According to the literature, the sedative effect of xenon has been observed by many researchers [2, 15-17]. When the xenon content in the gas mixture is higher than 20%, the psychotropic effect can persist for 48-80 hours [18]. Such a psychotropic effect creates comfortable conditions not only for the patient. For 57% of doctors, “difficult patients” with severe anxiety are the most stressful factor in their dental practice [19].

Changes in the parameters of central hemodynamics at different stages of the operation were multidirectional. In the first group (LA), the SBP, DBP and MAP did not significantly change statistically, and the heart rate increased after injection from 84.2 ± 5.0 to 92.6 ± 13.7 beats/min ($p < 0.050$). At subsequent stages of the operation, heart rate decreased and did not significantly differ statistically from the initial values. In all patients of groups 2 and 3, blood pressure indicators increased, and heart rate significantly decreased statistically ($p < 0.001$) after inhalation of xenon-oxygen mix, which may be associated with a pronounced cardioactive effect of xenon due to an increase in myocardial contractility and the absence of cardiotoxic effect, similar to other inhaled general anesthetics [3, 20].

After LA (stage “Injection”), MAP indices in patients of groups 2 and 3 returned to their initial values and did not significantly change statistically until the end of the operation. HR indices remained reduced compared with the initial values until the end of the operation ($p < 0,050$), which indicated the persistence of the cardioactive effect during the entire operation.

The initial indicators of the KI in the studied groups corresponded to the balanced sympathetic tonus and parasympathetic tonus and did not statistically significantly differ ($p > 0.500$). The KI was 1.1 ± 7.6% in the first group (LA), 0.6 ± 10.8% in the second group (Xe + LA), and -0.5 ± 8.1% in the third group (TENS + Xe + LA). After the administration of a local anesthetic solution, the KI statistically significantly increased ($p < 0.010$) in the first group (LA), reflecting an increase of the tonus of the sympathetic nervous system in response to the injection. After that, the KI decreased and did not significantly differ statistically from the initial value during all subsequent stages of the operation. However, a precollaptoid state was noted in three patients during the operation, which was characterized by dizziness, sonitus, and cold sweating. This was corrected by changing the position of the patient's body.

In groups 2 and 3, the KI decreased significantly in all patients after inhalation of xenon-oxygen mix, quantitatively corresponding to the state of parasympathicotonia on average. Clinically, warm skin and pink complexion were observed in patients. In both groups, the KI values after inhalation of xenon-oxygen mix remained statistically significantly ($p < 0.050$) reduced (compared to the initial values) until the end of the operation, reflecting the prolonged vegetotropic effect of xenon.

Comparison of groups showed that the KI values in both groups after inhalation of xenon-oxygen mix were statistically significantly ($p < 0.050$) lower than in the first group (LA) during all stages of the operation. However, at the final stage after the operation, significant differences were found only between the first (LA) and second (Xe + LA) groups of patients, while the KI values in the third group (TENS + Xe + LA) did not significantly differ statistically from the other two groups ($p > 0,500$). This indicates that TENS prevents the persistence of the vegetotropic effect of xenon.

Obtained results are consistent with the data of the study [21], in which the status of the autonomic nervous system was assessed using heart rate variability and an increase of the tonus of the parasympathetic nervous system under the influence of xenon was observed. An increase in the parasympathetic tonus reduces the risk of perioperative myocardial ischemia, which is especially important in patients with cardiovascular diseases.

Signs of nausea were observed in two of the 20 patients of group 2 (Xe + LA). This side effect of xenon – a higher risk of postoperative nausea and vomiting compared to other gaseous anesthetics – have been noted by other researchers [2]. According to our observations, a possible cause of this side effect is a significant and lasting increase of the tonus of the parasympathetic nervous system.

Figure 3 shows the KI dynamics in two patients (M and Yu) with a quantitatively identical reaction to the inhalation of xenon-oxygen mix at the Xe stage, after which the KI values were less than -34%, which corresponds to severe parasympathicotonia. Patient M was in group 2 (Xe + LA) and had signs of nausea. Before anesthesia ("Control" stage), KI values for this patient were -11.1%, which corresponded to increased parasympathetic tonus. After LA (stage "Incision"), KI values in this patient showed virtually no change until the end of the operation, which quantitatively corresponds to the state of parasympatheticotonia.

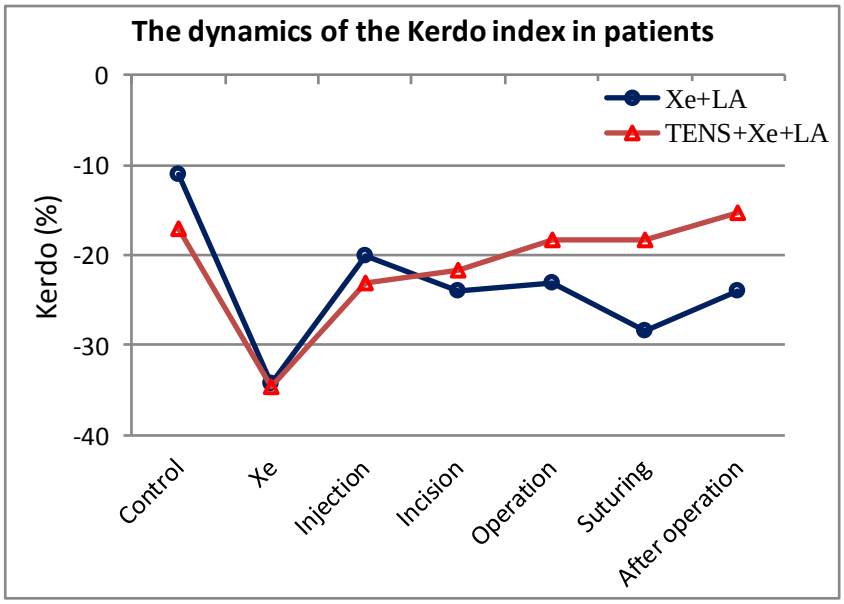


Figure 3. The dynamics of the KI at the stages of operation in patients who were anesthetized using xenon-oxygen mix inhalation and local anesthesia (Xe + LA) or a combination of transcutaneous electrical nerve stimulation, xenon-oxygen mix inhalation and local anesthesia (TENS + Xe + LA)

The second patient, Yu, was in group 3 (TENS + Xe + LA), and no side effects were observed in his case. Before anesthesia ("Control" stage), KI values for this patient were -17.1%, which corresponds to the increased parasympathetic tonus, similar to patient M. After LA (stage "Incision"), KI in this patient gradually increased and by the end of the operation, it was -15.4%, which corresponds to the normal tonus of the autonomic nervous system.

One of the possible reasons for the different dynamics of KI after inhalation of xenon-oxygen mix might be that TENS can activate the opioidergic antinociceptive system, the mechanisms of which involve the periaqueductal gray matter, which is also involved in the regulation of vegetative functions in response to emotionally significant stimuli [22]. This data shows that further development of methods for the use of xenon using means to control the tonus of the involuntary nervous system to prevent side effects is promising.

KI and HADS show the parameters of the state of patients, which are formed with the participation of the hypothalamus, a general structure of the central nervous system [23] that regulates both autonomic and emotional reactions. It could be expected that interrelations will be found between these indicators

due to the fact that xenon affects them through the hypothalamus. However, neither absolute values, nor their changes at the stages of the operation showed statistically significant interdependencies of these indicators. Based on this, it can be concluded that the observed psychotropic and vegetotropic effects of xenon-oxygen mix inhalation have different physiological mechanisms and are not determined by the involvement of the hypothalamus, as suggested by H. Yoshida [24].

An analysis of our results and literature data suggests that the psychotropic effect of xenon can occur due to the effect on the hippocampus, cerebral cortex, amygdala, and striatum, where the concentration of NMDA receptors is the highest [25-27]. Xenon significantly reduced excitation transfer via pathways with NMDA and AMPA receptors in the basolateral corpus amygdaloideum (which plays an important role in amnesia caused by anesthesia), without affecting inhibitory synaptic transmission [28]. This explains the anxiolytic effect of xenon, which reduced memories of negative events [4].

An increase in myocardial contractility (which is combined with the effects of central regulation of the tonus of the autonomic nervous system and is reflected in KI values) plays an important role in the mechanisms of the vegetotropic effect of xenon, which can be assessed using KI and heart rate indicators [3, 20].

A study of blood oxygen saturation (SpO_2) showed that its initial values in the studied groups did not have statistically significant differences ($p > 0.500$). In the first group (LA), SpO_2 decreased from the initial value of 97.9 ± 1.6% to 95.4 ± 1.3% ($p < 0.001$) at the injection stage, which indicated a decrease in tissue metabolism. However, during the subsequent stages of the operation, the SpO_2 returned to their original values. After inhalation of xenon-oxygen mix, SpO_2 increased ($p < 0.001$) and remained statistically significantly increased compared to the initial values until the end of the operation both in the second ($p < 0.001$) and the third ($p < 0.005$) groups.

A comparison between the studied groups showed that at all stages of the operation, the SpO_2 values in groups 2 and 3 were statistically significantly ($p < 0,050$) higher than in the first group (LA). After surgery, statistically significant ($p < 0.050$) differences were found only between group 1 (LA) and group 2 (Xe + LA). Consequently, obtained data indicates that TENS prevents the persistence of the effect of xenon on SpO_2 indices and KI.

According to the literature data, the increase in blood oxygen saturation occurs due to an increase in the expression of the factor (HIF-1α) during hypoxia, which leads to an increase in erythropoietin level and red blood cells count in the circulating blood, providing neuroprotective effect of xenon [29]. This effect can persist for more than 24 hours after inhalation of xenon-oxygen mix [30, 31], which ensures an improvement in tissue metabolism in the early postoperative period.

The most intense pain was experienced by patients of all studied groups during the operation at the "Injection" stage: 5.7 ± 1.3 VAS points (severe or very severe pain) in the first group (LA), 2.2 ± 0.7 VAS points (moderate or mild pain) in the second group (Xe + LA), and 1.0 ± 0.0 VAS points (mild pain) in the third group (TENS + Xe + LA). After administration of anesthesia, at the "Incision", "Operation", and "Suturing" stages, the amount of pain decreased significantly and was statistically significantly lower compared with the values at the "Injection" stage in all studied groups.

Assessment of the significance of differences between the groups showed that the VAS pain values at the "Incision" and "Operation" stages in the first group (LA) were significantly higher only compared to the third group (TENS + Xe + LA), and compared with the second group (Xe + LA) they did not differ. This suggests that the analgesic effect of xenon at these stages of the intervention was not sufficiently pronounced. Only at the "Suturing" stage, VAS pain value was statistically significantly ($p < 0.01$) lower in the second and third groups compared to the first group (LA).

The pronounced analgesic effect of multimodal analgesia in the third group (TENS + Xe + LA) occurred due to the fact that the used components acted together and affected different mechanisms of pain formation. TENS acted similarly to the "Gate control" mechanisms and also activated monoaminergic or opioidergic antinociceptive system. Inhalation of xenon-oxygen mix had an inhibitory effect on pain formation involving NMDA receptors, but without the involvement of the opioidergic antinociceptive system [32].

Reduced soreness at all stages of the operation made it possible to significantly reduce the consumption of local anesthetic for dental implantation in groups, for which xenon-oxygen mix inhalation was used. The consumption of local anesthetic during the operation was 1.7-2.55 ml (conduction and infiltration anesthesia) in the first group (LA), 0.93-1.78 ml in the second group (Xe + LA), and 0.42-1.27 ml in the third group (TENS + Xe + LA). Due to the low soreness in the third group (TENS + Xe + LA), the use of a simpler technique (only infiltration anesthesia) was sufficient for LA.

During the postoperative period, the amount of pain was assessed on the first, second and third day. The severity of edema was also evaluated in all patients of the studied groups on the third day. The results are presented in Table 5.

Table 5. VAS of pain (VAS pain) and VAS of edema (VAS edema) values during the postoperative period in studied groups

Group	Indicator	Postoperative period		
		First day	Second day	Third day
Group 1 (LA)	VAS pain	3.8±1.2	2.2±1.0	1.2±0.7
	VAS edema	-	-	2.1±0.8
Group 2 (Xe+LA)	VAS pain	1.9±0.6	1.0±0.6	0.5±0.5
	VAS edema	-	-	0.6±0.7
Group 3 (TENS+Xe+LA)	VAS pain	1.2±0.6	0.5±0.5	0.0±0.0
	VAS edema	-	-	0.6±0.5

In the first day, the amount of pain was 3.8 ± 1.2 VAS points (severe or moderate pain) in the first group (LA), 1.9 ± 0.6 VAS points (mild pain) in the second group (Xe + LA), and 1.2 ± 0.6 VAS points (mild pain) in the third group (TENS + Xe + LA). At this stage of treatment, the VAS pain values in the first group (LA) were statistically significantly ($p < 0.01$) higher than in the other groups, which indicates a pronounced prolonged effect of inhalation of xenon-oxygen mix. Of the 20 patients in the first group, 11 patients had VAS pain values of four points higher, which corresponds to severe pain. This data is consistent with estimates of the amount of pain after surgery in the maxillofacial region, which ranged from two to six points, four points on average [33]. The treatment of postsurgical pain syndrome is recommended when the amount of pain is four points or higher on a 10-point scale according to the recommendations (Postoperative Pain Management – Good Clinical Practice. General recommendations and principles for successful pain management. 2005).

A modern approach to the treatment of postsurgical pain syndrome is based on two concepts [34]:

1 – the concept of preventive analgesia;

2 – the concept of multimodal analgesia.

The use of xenon-oxygen mix inhalation and TENS allowed us to effectively implement not only potentiated intraoperative analgesia, but also the concept of preventive analgesia in the treatment of postoperative pain syndrome in our work.

In the next two days of observation, the amount of pain decreased in all groups. However, on the second and third days after the operation, VAS pain values in the first group (LA) were statistically significantly ($p <0.01$) higher than in the second and third groups. The formation of postoperative pain occurs in two stages (8). The pathophysiological basis of the pain syndrome in the first stage is an excessive increase in the sensitivity (receptor upregulation) of nociceptors – primary hyperalgesia; bradykinin plays an important role in its mechanisms. Study results indicate that at all stages of the operation and in the postoperative period, VAS pain values were statistically significantly lower only the third group (TENS + Xe + LA) compared to the first group (LA). We can assume that the use of TENS prevented the development of primary hyperalgesia due to inhibition of excitation transfer from nociceptors to primary transmitting neurons.

The central mechanisms of upregulation of nociceptive neurons involving NMDA receptors are utilised at the second stage of the formation of postoperative pain syndrome (secondary hyperalgesia). This process takes 12–18 hours, which in a significant percentage of cases, leads to an increase in the intensity of postoperative pain on the second day after surgery (8). It can be assumed that the statistically significantly reduced VAS pain values in second and third groups compared with the first group (LA) were due to the effect of xenon.

Assessment of the degree of tissue edema on the third day of the postoperative period showed that its severity was 2.1 ± 0.8 VAS points in the first group (LA), which corresponded to edema in the mucobuccal fold with the formation of visible edema in the soft tissues of the face in some cases. In the second group (Xe + LA), the quantitative values of edema were 0.6 ± 0.7 points on average: edema was localized in the flap area and it spread to the mucobuccal fold area only in two patients out of 20. In the third group (TENS + Xe + LA), VAS edema values were 0.6 ± 0.5 points. In this group, half of the patients did not have tissue edema, and in none of the patients the edema spread to the area of the mucobuccal fold. It is likely that due to the low amount of pain and the absence of tissue edema, two patients did not consider it necessary to visit a doctor for examination in the postoperative period, and, as a result, the number of patients examined at this stage in the third group was lower.

A significant decrease in the degree of edema in groups 2 and 3 was probably caused by the reduced intensity of the pain syndrome, which did not cause a spasm of peripheral blood vessels, as well as by a pronounced vegetotropic effect of xenon-oxygen mix

inhalation, which lead to an increase in the parasympathetic tonus and blood oxygen saturation in all patients.

It should also be noted that the period of adaptation and integration of implants proceeded without complications in all patients. There were no differences between the studied groups during the postoperative period in the early stages.

The results and their analysis allowed us to evaluate the adequacy of anesthesia using xenon. The main requirements for the adequacy of anesthesia are:

- achievement of an effective analgesic effect that prevents the occurrence of intense pain;
- relief of feelings of fear, anxiety and psycho-emotional reactions, which are expressed in patients in dentistry to a larger extent compared to other types of operations and the most common fears of people [19];
- stabilization of indicators of central hemodynamics, external and tissue respiration while maintaining protective reflexes of the respiratory tract to prevent vegetative reactions that can cause the development of emergency conditions.

An additional requirement for the quality treatment of dental diseases on an outpatient basis is the preservation of the patient's consciousness and verbal contact with them.

The most acceptable method of stopping vegetative reactions, anxiety and fear in patients in dentistry is conscious sedation [19, 35], which is considered as moderate sedation according to the classification of the American Society of Anesthesiologists. Sedation with preserved consciousness is defined as the minimum degree of depression of consciousness, in which the patient retains the ability to independently and continuously maintain breathing and adequately respond to physical irritation or verbal commands. Consciousness sedation is achieved using the medicated or non-medicated methods, or their combination. The recommendation to use conscious sedation instead of general anesthesia on an outpatient basis was adopted by the International Federation of Dental Anesthesiology Societies – IFDAS (2003) and The European Federation for the Advancement of Anaesthesia in Dentistry – EFAAD (2010). However, this recommendation does not indicate that this technique is the most effective and safe way to conduct sedation. The literature data [2, 3, 7, 20, 21, 32] and the results of this study suggest that the use of xenon is a promising way to create such a method.

IV. CONCLUSIONS

The results show that multimodal anesthesia using TENS, xenon-oxygen mix inhalation, and LA provides adequate anesthesia for patients, has pronounced and prolonged analgesic, psychosedative, and vegetotropic effects, reduces the risk of exigent conditions and postoperative complications, and creates comfortable conditions for the patient and the dentist. To prevent the side effect of xenon in the form of a higher risk of developing postoperative nausea and vomiting, it is advisable to control the parasympathetic tonus of the autonomic nervous system, which increases significantly after xenon-oxygen mix inhalation. At the intraoperative stage of dental implantation, it is necessary to use combined anesthesia to potentiate the analgesic effect.

Comparing the possible mechanisms of the effect of multimodal anesthesia, one can agree with the opinion of Winkler [32] that the effect of xenon is not characterized by an effect on individual structural and functional systems that form pain sensitivity, psychoemotional reactions, or the regulation of autonomic functions. Due to the effects on the molecular level, xenon creates various conditions characterized by a complex change in the functioning of body systems. In this regard, the study of the characteristics of xenon and the development of methods for its use in clinical practice, as well as conduction of multi-parameter studies with monitoring of complexes of indicators (and not individual indicators) are promising.

REFERENCES

[1] A.A. Kulakov, T.G. Robustova, A.I. Nerobeev. Zubnaya i chelyustno-litsevaya implantatsiya [Dental and maxillofacial implantation]. Khirurgicheskaya stomatologiya i chelyustno-litsevaya khirurgiya. Natsionalnoe rukovodstvo [Surgical dentistry and maxillofacial surgery. National manual.]. GEOTAR-media publishing group, pp. 865-889, 2010.

[2] L.S.C. Law, E.A.G. Lo, T.J. Gan. Xenon anesthesia: a systematic review and meta-analysis of randomized controlled trials. Anesthesia & Analgesia, vol. 122, pp. 78-97, 2016.

[3] N.E. Burov, V.N. Potapov, G.N. Makeev. Ksenon v anesteziologii. Kliniko-eksperimentalnye issledovaniya [Xenon in anesthesiology. Clinical and experimental studies]. Moscow: Pulse, 2000.

[4] E.G. Meloni, T.E. Gillis, J. Manoukian, M.J. Kaufman. Xenon impairs reconsolidation of fear memories in a rat model of post-traumatic stress disorder (PTSD). PLoS ONE., vol. 9, no. 8, 2014.

[5] J. D. Deken, S. Rex, D. Monbaliu, J. Pirenne, I. Jochmans. The efficacy of noble gases in the attenuation of ischemia reperfusion injury: a systematic review and meta-analyses. Critical Care Medicine, vol. 44, no. 9, pp. 886-896, 2016.

[6] M. Maze. Preclinical neuroprotective actions of xenon and possible implications for human therapeutics: a narrative review. Canadian journal of anesthesia – Journal canadien d'anesthésie, vol. 63, pp. 212-226, 2016.

[7] E. Esencan, S. Yuksel, Y.B. Tosun, A. Robinot, I. Solaroglu, J.H. Zhang. Xenon in medical area: emphasis on neuroprotection in hypoxia and anesthesia. Medical Gas Research, vol. 3, no. 4, 2013.

[8] W. Liu, Y. Liu, H. Chen, K. Liu, H. Tao, X. Sun. Xenon preconditioning: molecular mechanisms and biological effects. Medical Gas Research, vol. 3, no. 3, 2013.

[9] O.N. Moskovets. Elektrofiziologicheskii analiz antinotsitseptivnykh effektov elektrostimulyatsii ushnoi rakoviny u koshek. [Electrophysiological analysis of the antinociceptive effects of electrostimulation of the auricle in cats]. PhD Thesis in Biology sciences. Moscow, 1980.

[10] I.A. Shugailov. Povyshenie effektivnosti obezbolivaniya pri khirurgicheskom lechenii stomatologicheskikh zabolevnii [Improving the effectiveness of analgesia in the surgical treatment of dental diseases]. PhD Thesis in Medicine sciences. Moscow, 1984.

[11] Medical technology: "The use of oxygen-xenon mix for pain and pain syndromes." Permit for use MT FS № 2010/123, April 2, 2010.

[12] Medical technology: "A method for the correction of acute and chronic stress disorders based on the inhalation of therapeutic doses of medical xenon." Permit for use MT FS № 2010/227, June 17, 2010.

[13] I.A. Shugailov, A.S. Babikov, N.E. Burov, M.V. Kolesnichenko, O.N. Moskovets, I.V. Molchanov, A.A. Nikitin, A.E. Olesov, D.N. Rodionov, A.V. Potapov, V.N. Potapov, S.V. Potapov, D.K. Yudin. Primenenie meditsinskogo ksenona pri kombinirovannom obezbolivanii i sedatsii v ambulatornoi stomatologicheskoi praktike [The use of medical xenon in combined anesthesia and sedation in outpatient dental practice]. Metodicheskie rekomendatsii, 2015.

[14] A.S. Zigmond, R.P. Snaith. The Hospital Anxiety and Depression scale. Acta Psychiatrica Scandinavica, vol. 67, pp. 361-370, 1983.

[15] A. Dobrovolsky, T.E. Ichim, D.Ma, S. Kesari, V. Bogin. Xenon in the treatment of panic disorder: an open label study. Journal of Translational Medicine, vol. 15, no. 137, 2017.

[16] A.S. Kalmanov, Yu.A. Bubeev, T.I. Kotrovskaya. Vliyanie kursovogo primeneniya ingalyatsii ksenono-kislorodnoi gazovoi smesi na pokazateli funktsionalnogo sostoyaniya alpinistov. [Course application effect of oxygen-xenon gas mix inhalation on functional status of mountaineers]. Lechebnaya fizkultura i sportivnaya meditsina, vol. 3, no. 87, pp. 27-34, 2011.

[17] T.V. Igoshina. Psikhofiziologicheskoe obosnovanie primeneniya metoda ingalyatsii ksenona pri korrektsii nevroticheskikh, svyazannykh so stressom rasstroistv u lits opasnykh professii [Psychophysiological substantiation for the use of the xenon inhalation method in the correction of neurotic stress-related disorders in persons of dangerous professions]. PhD Thesis in Medicine sciences. Moscow, 2017.

[18] V.I. Sovetov, O.P. Mikheev, E.S. Andreeva, N.E. Ivanova, A.G. Vinokurov, N.A. Kurkin. Sposob povysheniya fizicheskoi rabotosposobnosti cheloveka [A way to increase the physical performance of a person]. Russian patent No. 2466750. 20.11.2012.

[19] S.F. Malamed. Sedation: a guide to patient management. Elsevier, 2018.

[20] N.E. Burov, V.N. Potapov. Ksenon v meditsine: ocherki po istorii i primeneniyu meditsinskogo ksenona. [Xenon in medicine: essays on the history and application of medical xenon]. Moscow: Pulse, 2012.

[21] R. Hanss, B. Bein, P. Turowski, E. Cavus, M. Bauer, M. Andretzke, M. Steinfath, J. Scholz, P. H. Tonner. The influence of xenon on regulation of the autonomic nervous system in patients at high risk of perioperative cardiac complications. British Journal of Anaesthesia, vol. 96, no. 4, pp. 427-436, 2006.

[22] R. Dampney. Emotion and the Cardiovascular System: Postulated Role of Inputs from the Medial Prefrontal Cortex to the Dorsolateral Periaqueductal Gray. Frontiers in Neuroscience, vol. 12, p. 343, 2018.

[23] R. Dampney. Central mechanisms regulating coordinated cardiovascular and respiratory function during stress and arousal. Journal of Physiology - Regulatory, Integrative and Comparative Physiology, vol. 309, pp. 429-443, 2015.

[24] H. Yoshida, T. Kushikata, T. Kubota, K. Hirota, H. Ishihara, A. Matsuki. Xenon inhalation increases norepinephrine release from the anterior and posterior hypothalamus in rats. Canadian Journal of Anesthesia, vol. 48, pp. 651-655, 2001.

[25] W.F. Maragos, J.B. Penney, A.B. Young. Anatomic correlation of NMDA [3H]-TCP-labelled receptors in rat brain. Journal of Neuroscience, vol. 8, no. 2, pp. 493-501, 1988.

[26] H.M. Homi, N. Yokoo, D.Ma, D.S. Warner, N.P. Franks, M. Maze, H.P. Grocott. The neuroprotective effect of xenon administration during transient middle cerebral artery occlusion in mice. Anesthesiology, vol. 99, pp. 876-881, 2003.

[27] D. Ma, M. Hossain, G.K. Pettet, Y. Luo, T. Lim, S. Akimov, R.D. Sanders, N.P. Franks, M. Maze. Xenon preconditioning reduces brain damage from neonatal asphyxia in rats. Journal of Cerebral Blood Flow & Metabolism, vol. 2, no. 26, pp. 199-208, 2006.

[28] R. Haseneder, S. Kratzer, E. Kochs, V.-S. Eckle, W. Zieglga, G. Rammes. Xenon reduces N-methyl-D-aspartate and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor–mediated synaptic transmission in the amygdala. Anesthesiology, vol. 109, pp. 998-1006, 2008.

[29] A. Alam, K. C. Suen, Z. Hana, D. Robert, R. D. Sanders, M. Maze, D. Ma. Neuroprotection and neurotoxicity in the developing brain: an update on the effects of dexmedetomidine and xenon. Neurotoxicology and Teratology, vol. 60, pp. 102-116, 2017.

[30] C. Stoppe, J. Ney, M. Brenke, A. Goetzenich, C. Emontzpohl, G. Schälte, O. Grottke, M. Moeller, R. Rossaint, M. Coburn. Sub-anesthetic xenon increases erythropoietin levels in humans: a randomized controlled trial. Sports Medicine, vol. 46, pp. 1753-1766, 2016.

[31] C. Frampas, M. Augsburger, V. Varlet. Xenon: from medical applications to doping uses. Toxicologie Analytique & Clinique, vol. 29, no. 3, pp. 309-319, 2017.

[32] D.A. Winkler, A. Thornton, G. Farjot, I. Katz. The diverse biological properties of the chemically inert noble gases. Pharmacology & Therapeutics, vol. 160, pp. 44-64, 2016.

[33] H.J. Gerbershagen, S. Aduckathil, A.J. van Wijck, L.M. Peelen, C.J. Kalkman, W. Meissner. Pain intensity on the first day after surgery: a prospective cohort study comparing 179 surgical procedures. Anesthesiology, vol. 118, no. 4, pp. 934-944, 2013.

[34] A.M. Ovechkin. Posleoperatsionnaya bol: sostoyanie problemy i sovremennye tendentsii posleoperatsionnogo obezbolivaniya. [Postoperative pain: the status of the problem and current trends in postoperative pain management]. Regionarnaya anesteziya i lechenie ostroy boli, vol. 9, no. 2, pp. 29-39, 2015.

[35] N.M. Girdler, C.M. Hill, K.E. Wilson. Conscious Sedation for Dentistry. Second Edition John Wiley & Sons, 2018.