Research Article

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Effects of Xenon on Neuroinflammatory Markers: a Prospective Pilot Study

A.I. Shpichko[1, 2], R.A. Cherpakov[1, 3] ✉, A.K. Shabanov[1, 3], A.K. Evseev[3], I.V. Goroncharovskaya[3], O.A. Grebenchikov[1, 4]

Laboratory of Organ Protection in Critical Conditions
[1] Federal Scientific and Clinical Center for Resuscitation and Rehabilitation, V.A. Negovsky Research Institute of General Reanimatology
25, bldg. 2, Petrovka Str., 107031, Moscow, Russian Federation
[2] Peoples' Friendship University of Russia
6, Miklukho-Maklaya Str., 117198, Moscow, Russian Federation
[3] N.V. Sklifosovsky Research Institute for Emergency Medicine
3, Bolshaya Sukharevskaya Sq., 129090, Moscow, Russian Federation
[4] M.F. Vladimirsky Moscow Regional Research Clinical Institute
61/2, Shchepkina Str., 129110, Moscow, Russian Federation

✉ **Contacts:** Rostislav A. Cherpakov, Researcher, Laboratory of Organ Protection in Critical Conditions, V.A. Negovsky Research Institute of General Reanimatology, Federal Scientific and Clinical Center for Resuscitation and Rehabilitation. Email: zealot333@mail.ru

ABSTRACT The leading role of neuroinflammation as the culprit of a long-term impairment of consciousness in patients after injuries to the central nervous system forces us to look for new effective strategies for resolving this pathological process. Xenon reducing the intensity of the inflammatory response due to the impact on several links is potentially able to have a beneficial effect on this category of patients. Using laboratory equipment, we evaluated the effect of half-hour daily inhalations of a 30% air mixture with 30% xenon for 7 days on the level of markers of neuronal damage and regeneration of nervous tissue.

AIM To study the effect of inhalation of an air-xenon mixture on the dynamics of markers of neuroinflammation and restoration of nervous tissue in patients after traumatic brain injury (TBI).

MATERIAL AND METHODS We conducted a prospective randomized clinical trial evaluating the effect of inhaled xenon for sedation on the level of consciousness and spasticity in patients with prolonged post-coma impairment of consciousness. Patients were randomized into 2 equal groups. In Group I (Comparison, n=15) in addition to the standard treatment for TBI, each patient included in the study underwent 7 sessions of inhalation of an air mixture with an oxygen content of at least 30 vol.% for 30 minutes. In Group II (Xenon, n=15) in addition to the standard treatment, each patient included in the study underwent a half-hour inhalation with an air-xenon gas mixture (with a xenon content of 30 vol.% and oxygen — 30 vol.%) for 7 days, 1 time per day. The levels of interleukin-6, α-1 acid glycoprotein (AGP), S100 b protein and brain-derived neurotrophic factor were assessed before the first treatment and then once a day for 6 days.

RESULTS The final evaluation included 12 patients from the Comparison Group and 12 patients from the Xenon Group. The greatest difference in the concentration of interleukin-6 between the Comparison and Xenon Groups was noted on the 5th day - 12.31 (10.21; 15.43) pg/ml vs. 7.93 (3.61; 9.27) pg/ml, respectively; however, the findings only tended to be statistically significant (p=0.07). When assessing the AGP level, the maximum difference was noted on the 4th day. In the Comparison Group, the AGP level was 0.81 (0.74; 0.92) pg/ml versus 0.614 (0.4; 0.79) pg/ml in the Xenon Group. And again, the data showed only a trend towards statistical significance (p=0.09). The highest level of brain-derived neurotrophic factor in the Xenon Group was observed on the 3th day — 0.1271 (0.046; 0.2695) pg/ml, which was statistically significantly higher than the one in the Comparison Group — 0.062 (0.036; 0.121) pg/ml (p=0.04). The concentration of S100 b protein during the entire observation period in both groups did not exceed 0.005 pg/ml.

CONCLUSION Xenon inhalation according to the method proposed by the authors had a beneficial effect on the processes of neural tissue regeneration, however, with regard to neuroinflammation, its effects were not so pronounced.

Keywords: xenon, prolonged impairment of consciousness, neuroinflammation, neuroprotection, rehabilitation

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Affiliations

Andrey I. Shpichko	Candidate of Medical Sciences, Senior Researcher, Laboratory of Organ Protection in Critical Conditions, V.A. Negovsky Research Institute of General Reanimatology, Federal Scientific and Clinical Center for Resuscitation and Rehabilitation; Associate Professor, Department of Anesthesiology and Resuscitation with the Course of Medical Rehabilitation, Peoples' Friendship University of Russia; https://orcid.org/0000-0002-4652-3259, shpichko.a@yandex.ru; 25%, completion of the clinical part of the study
Rostislav A. Cherpakov	Researcher, Laboratory of Organ Protection in Critical Conditions, V.A. Negovsky Research Institute of General Reanimatology, Federal Scientific and Clinical Center for Resuscitation and Rehabilitation; Junior Researcher, Department of General Resuscitation, N.V. Sklifosovsky Research Institute for Emergency Medicine; https://orcid.org/0000-0002-0514-2177, zealot333@mail.ru; 20%, editing of original material

Aslan K. Shabanov	Doctor of Medical Sciences, Chief Researcher, Laboratory of Clinical Pathophysiology in Critical Conditions, V.A. Negovsky Research Institute of General Reanimatology, Federal Scientific and Clinical Center for Resuscitation and Rehabilitation; Deputy Chief Physician for Anesthesiology and Resuscitation, N.V. Sklifosovsky Research Institute for Emergency Medicine; https://orcid.org/0000-0002-3417-2682, aslan_s@mail.ru; 17%, text editing, preparing text for publication
Anatoly K. Evseev	Doctor of Chemical Sciences, Leading Researcher, Department of General Resuscitation, N.V. Sklifosovsky Research Institute for Emergency Medicine; https://orcid.org/0000-0002-0832-3272, anatolevseev@gmail.com; 14%, data analysis
Irina V. Goroncharovskaya	Candidate of Chemical Sciences, Senior Researcher, Department of General Resuscitation, N.V. Sklifosovsky Research Institute for Emergency Medicine; https://orcid.org/0000-0003-0113-306X, goririna22@gmail.com; 12%, data analysis
Oleg A. Grebenchikov	Doctor of Medical Sciences, Chief Researcher, Laboratory of Organ Protection in Critical Conditions, V.A. Negovsky Research Institute of General Reanimatology, Federal Scientific and Clinical Center for Resuscitation and Rehabilitation; Leading Researcher, Department of Intensive Care, M.F. Vladimirsky Moscow Regional Research Clinical Institute (MONIKI); https://orcid.org/0000-0001-9045-6017, oleg.grebenchikov@yandex.ru; 12%, concept of the article, editing of primary material, final approval of the text

AGP - α-1 acid glycoprotein
CDC - chronic disorders of consciousness
IL-6 - interleukin-6
TBI - traumatic brain injury

INTRODUCTION

In the structure of traumatic brain injury (TBI) consequences, chronic disorders of consciousness (CDC) occupy an important place. CDC are conditions that develop after severe brain damage of traumatic and non-traumatic origin and are characterized by the recovery of wakefulness after coma, which is not accompanied by the recovery of consciousness [1, 2]. Data on the prevalence of the vegetative state in different countries according to the results of some studies range from 0.6 to 10%, on average 7% [3], according to other sources - 2.7% [4]. Of course, this problem is not as acute as high mortality rate after head injuries [5, 6], but it is one of the leading causes of persistent disability and the high cost of treatment and rehabilitation of this category of patients [7]. Even with a positive response to therapy applied within the existing standards [8, 9], there is a fairly high chance of prolonged disablement and, as a result, growing socio-economic losses. In their work, A.A. Belkin et al. covered the current state of the art in the diagnosis and treatment for prolonged impairment of consciousness in as much detail as possible. However, although the principles of diagnosis described in the article fully correspond to the modern understanding of the problem, as for the treatment, the authors, as in all previous works, adhere to a strategy aimed at rehabilitation and care [10]. This tactic is fully justified due to the lack of a drug with proven neuroprotective activity to date [11, 12]. A more complete understanding of the processes underlying prolonged impairment of consciousness helped to partly approach the solution of this problem (Fig. 1). The main role in the persistent neurological deficit belongs to neuroinflammation [13, 14], which prevents, among other things, the restoration of consciousness, and also contributes to the development of a number of complications, from cognitive impairment to Parkinson's and Alzheimer's diseases [15]. When considering the mechanisms of secondary damage as a result of TBI, it can be seen that the leading role is played by both excitotoxicity (with damage to NMDA receptors), and the formation of reactive oxygen species, nitric oxide, and disorders of calcium metabolism [16, 17].

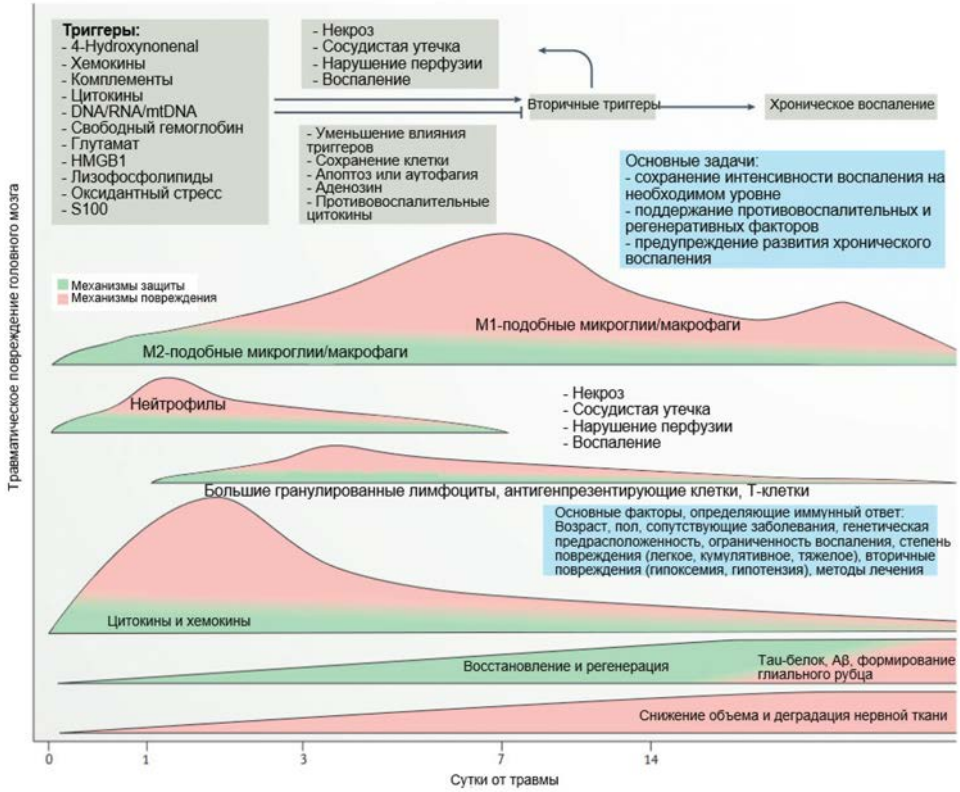

Fig. 1. Neuroinflammation after traumatic brain injury. Primary mechanical damage to the central nervous system can lead to the destruction of cell membranes, breaches in a blood vessels, and blood-brain barrier breakdown; which is accompanied by secondary reactions: ionic imbalance, release of active amino acids, calcium overload and mitochondrial dysfunction resulting in cell death. Primary and secondary injuries lead to the release of damage-associated molecular structures of cytokines and chemokines, as well as the activation of microglia, astrocytes, and the recruitment of circulating immune cells to the site of injury [18]

Of the known drugs that can, if not prevent, then at least partially slow down the development of these processes, xenon can be distinguished [19, 20]. As an inert gas, it is intact in relation to the body's homeostasis system, without being metabolized and excreted from the body unchanged. Its neuroprotective properties were shown both in the model of acute conditions (ischemic stroke, circulatory arrest) [21, 22] and in case of prolonged inflammation [23, 24], which served as the basis for evaluating its effects in prolonged impairment of consciousness. Given the timing of the course of pathological processes, as well as the fluctuating level of consciousness, when assessing the dynamics of the state in this category of patients, it is important to focus not only on clinical, but also on biochemical parameters. To assess the severity of damage to the nervous tissue and the intensity of neuroinflammation, we chose the two most widely used markers — interleukin-6 (IL-6) [25, 26] and α-1 acid glycoprotein (AGP) [27]. IL-6, despite its dichotomous effects on nervous tissue, is a fairly widely used biomarker of inflammation; however, many researchers note an increase in its level in patients with chronic neurological diseases accompanied by neuroinflammation — Alzheimer's disease and multiple sclerosis [28]. AGP as a marker of the intensity of inflammation of various origins is used in a fairly wide range of pathologies. Its concentration increases in response to adverse effects and damage by 10–100 times. Given that the exclusion criteria were the absence of infectious inflammatory processes, a high concentration of AGP was interpreted as persistent low-intensity neuroinflammation [29]. The S100 b protein, for all its informative value in the phase of acute inflammation, still did not have sufficient sensitivity and specificity in the framework of the studied pathology, however, the available data on its high level in the case of neurodegenerative processes led to its evaluation in parallel with other markers [30, 31]. In addition to assessing the level of damage and intensity of neuroinflammatory processes, it was also important to evaluate the effect of xenon on the processes of brain neurogenesis. For this purpose, the level of brain-derived neurotrophic factor (BDNF) was chosen [32, 33].

Aim: to study the effect of inhalation of an air-xenon mixture on possible pathways of neuroinflammation and the marker of nerve tissue recovery in patients after TBI.

MATERIAL AND METHODS

The authors present a prospective randomized clinical trial of the effect of xenon inhalation on the dynamics of biochemical markers of neuroinflammation and restoration of nervous tissue in patients with post-coma prolonged impairment of consciousness. The research was conducted within the framework of the current theme of the state assignment No. 075-01414-20-02 "Anesthetic neuroprotection with xenon and sevoflurane in severe brain damage. Clinical and experimental study" and was approved by the local ethical committee (Minutes of the meeting of the ethical committee 4/21/2 dated 09.29.21, No. 427/04.10.2021).

The patients were randomized into 2 equal groups (Fig. 2). In group I (Comparison, n=15), patients received standard treatment within the current protocols for the provision of care for CDC after TBI. In addition to standard therapy, patients of the Comparison group underwent 7 sessions of inhalation of an air-oxygen mixture with an oxygen content of at least 30 vol% for 30 minutes. In group II (Xenon, n=15), patients also received standard treatment, however, in addition to it, each patient underwent a half-hour inhalation of an air-xenon mixture (xenon content - 30 vol%, oxygen content - 30 vol%) for 7 days 1 time per day. The levels of IL-6, AGP, S100 b protein and brain-derived neurotrophic factor were assessed prior to the first procedure and then once a day for 6 days.

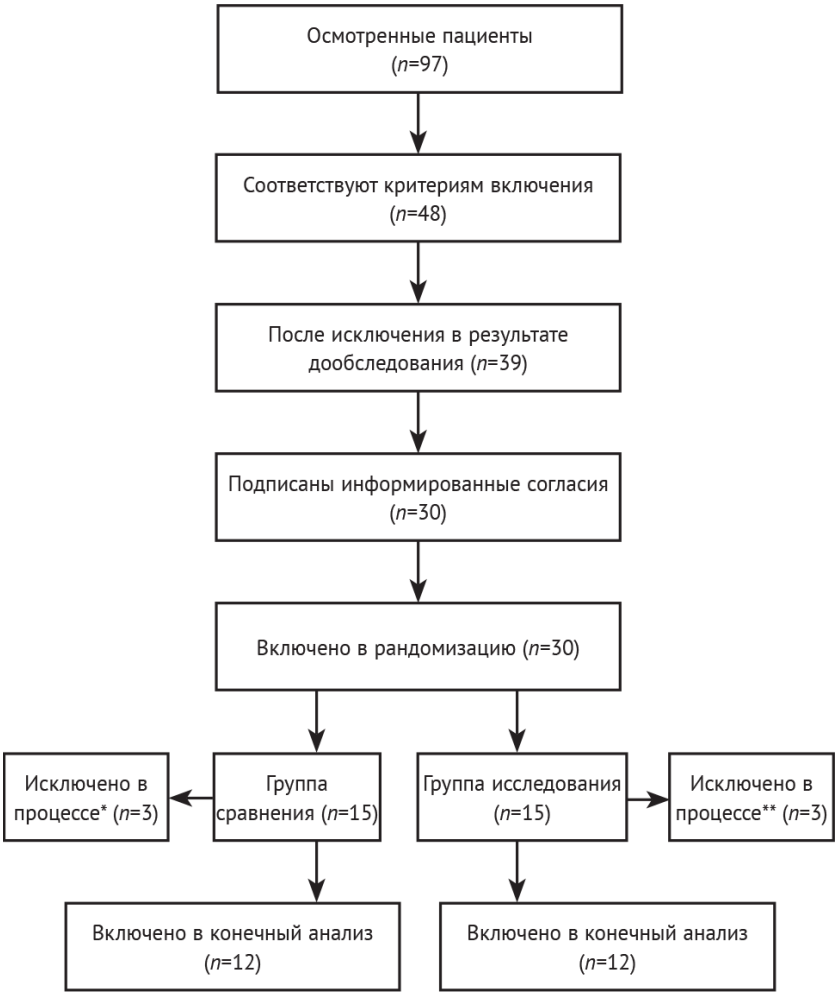

Fig. 2. Block diagram of the research's inclusion and exclusion

Notes: * — In one case, emergency surgical treatment of gastrointestinal bleeding was required, in 2 cases — the need for mechanical ventilation. ** — In 2 cases, inotropic support was required, and in one case, bypass surgery was required due to increased intracranial pressure

The recruitment of patients into the groups was carried out according to inclusion and exclusion criteria.

Inclusion Criteria:

- men and women aged 18 to 65;
- patients with severe brain damage due to TBI;
- level of consciousness: vegetative state or state of minimal consciousness;
- independent breathing;
- informed consent of the patients or their legal representatives to participate in the research.

Exclusion Criteria:

- indications for surgical emergency;
- need for inotropic and vasopressor support, VIS (vasoactive inotropic score) ⩾ 10;
- aggravated allergic history;
- drug intolerance;
- infectious process of any localization

— The researcher may decide to early terminate the patient's participation in the trial at any time if the patient's condition requires this.

In order to eliminate preferences of the researchers, the recruitment into the groups was carried out by the sealed envelope system.

After the start of the study, 3 patients were excluded from the Comparison group - in one case, emergency surgery for gastrointestinal bleeding was required, in 2 cases, the need for mechanical ventilation. 3 patients were also excluded from the Xenon group: in 2 cases, inotropic support was required, and in one case, bypass surgery was indicated due to increased intracranial pressure. The age and gender composition of the patients included in the study is presented in the table.

Table

Composition of Comparison and Xenon Groups

Comparison group, mean age 31.4±11.5 years			
Patient age, years	Males	Females	Total
18–30	3	2	5
31–40	1	2	3
41–50	3	1	4
Total	7	5	12
Xenon group, mean age 32.5±12.5 years			
Patient age, years	Males	Females	Total
18–30	4	1	5
31–40	3	2	5
41–50	2	0	2
Total	9	3	12

Note: The groups were comparable in terms of mean age, comorbid background, and methods of standard therapy used

For the procedure in both groups, a xenon therapeutic circuit (KTK-01) (Akela-N, Russia) was used, equipped with an oxygen and xenon gas analyzer, as well as a xenon dispenser that allows researchers to control both its current and total consumption. All the patients included in the trial breathed spontaneously through a tracheostomy tube. Before the procedure, the patient's tracheostomy tube was sanitized and the cuff was inflated to further seal the respiratory circuit and minimize xenon loss during inhalation.

In the Comparison group, inhalation with an oxygen-air mixture was carried out according to the following method: after connecting the patient to the xenon therapeutic circuit, five-minute denitrogenation was performed by inhaling 100% oxygen until a stable oxygen concentration in the circuit - 95–97 vol% - was reached. After that, the oxygen concentration was reduced to 30 vol%, and the exhalation valve was closed, thereby

making the circuit completely closed. Within 30 minutes, the patient inhaled an oxygen-air mixture while the constant oxygen concentration of 30 vol% was being maintained. During the procedure, 3-lead electrocardiography monitoring with the calculation of heart rate and blood pressure by a non-invasive method, as well as pulse oximetry plethysmography were carried out. After 30 minutes, the therapy circuit was disconnected and the procedure ended.

In the Xenon group, denitrogenation was performed according to the same method, however, immediately after the exhalation valve was closed, xenon was supplied to the circuit at a rate of 0.5–1 l/min until a concentration of 30 vol.% was reached. Further, the indicated concentration was maintained for 30 minutes with the monitoring similar to that in the Comparison group. After the end of the procedure, oxygen was supplied to the circuit at a rate of 3–5 l/min, and the exhalation valve was opened. Within 2–3 minutes, the xenon concentration in the exhaled mixture was brought to zero, after that the patient was disconnected from the circuit.

The level of IL-6, AGP, S100 b and BDNF was determined in venous blood collected from a peripheral vein.

Statistical data analysis was carried out using the Statistica 10 software package (StatSoft, Inc., USA). Descriptive statistics of quantitative traits are presented as medians and quartiles in Me (LQ; UQ) format. The study groups were compared using the Mann–Whitney U test and the Wilcoxon signed-rank test. Differences were considered statistically significant at $p<0.05$.

RESULTS

The initial level of IL-6 in the Comparison group was 13.85 (7.88; 17.43) pg/ml, not statistically significantly different from its level in the Xenon group — 14.34 (6.7; 16.33) pg/ml ($p>0.05$). When evaluating the dynamics of this marker, the greatest difference was noted on the 5th day — 12.13 (8.44; 16.81) pg/ml in the Comparison group versus 7.93 (3.61; 9.27) pg/ml in case of xenon inhalation ($p=0.07$) (Fig. 3). AGP levels before the start of the therapy also did not differ significantly - 0.79 (0.54; 1.15) pg/ml in the Comparison group versus 0.83 (0.72; 1.287) pg/ml in case of xenon inhalation ($p >0.05$). The greatest difference was noted by day 4 — 0.81 (0.63; 1.04) pg/ml in the Comparison group, and 0.614 (0.4; 0.79) pg/ml in the Xenon group ($p=0.09$) (Fig. 4). Unlike biomarkers of neuroinflammation, the dynamics of BDNF was statistically significant. The initial level of neurotrophic factor in the Comparison group was 0.022 (0.018; 0.027) pg/ml, and in the Xenon group - 0.0215 (0.019; 0.05148) pg/ml ($p>0.05$). A statistically significant difference was observed on the 3rd day — 0.054 (0.021; 0.093) pg/ml in the Comparison group versus 0.1271 [0.046; 0.2695] pg/ml in the Xenon group ($p=0.04$) (Fig. 5). The level of S100 b protein in both groups during the entire observation period did not exceed 0.005 pg/ml, being not statistically significant and not exceeding the reference values.

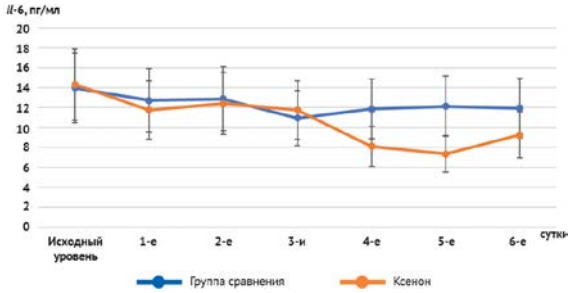

Fig. 3. Dynamics of the IL-6 level in the blood of patients with prolonged impairment of consciousness

Note: A certain trend towards a statistically significant decrease in the IL-6 level in the Xenon Group as compared to the Comparison Group was noted on the 5th day ($p=0.07$). Also, by the 5th day, there was a certain trend towards a statistically significant decrease in the IL-6 level as compared to the initial one ($p=0.07$)

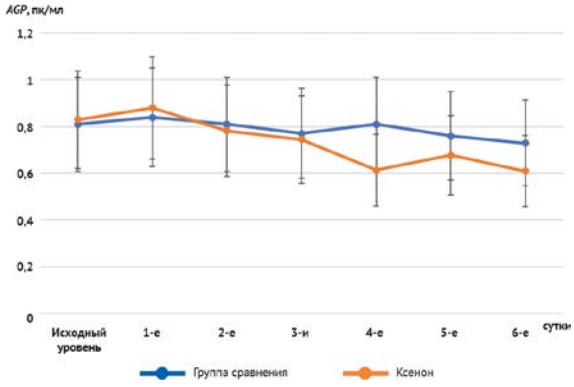

Fig. 4. Dynamics of the α-1 acid glycoprotein (AGP) level in the blood of patients with prolonged impairment of consciousness

Note: A certain trend towards a statistically significant decrease in the AGP level in the Xenon Group as compared to the Comparison Group was noted on the 4th day ($p=0.09$). Also, by the 4th day, there was a certain trend towards a statistically significant decrease in the AGP level compared to the initial one ($p=0.09$)

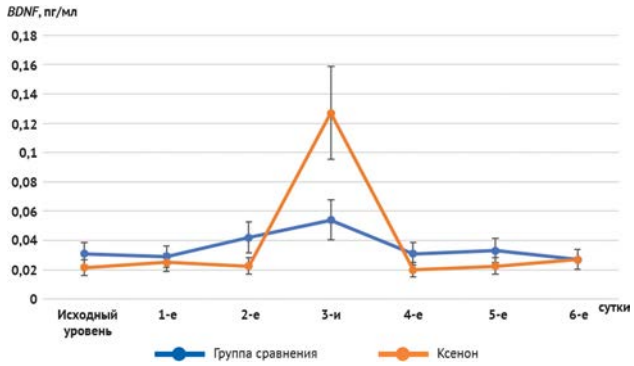

Fig. 5. Dynamics of the BDNF level in the blood of patients with prolonged impairment of consciousness

Notes: By the 3rd day in the Xenon Group, there was an almost sixfold increase in the BDNF level, which statistically significantly exceeded both its initial level (p=0.035) and the values in the Comparison Group on the 3rd day (p=0.04)

CONCLUSION

Influencing key factors of neuroinflammation may be the key to solving the problem of proloned impairment of consciousness. Modern medicine has solved a huge number of problems associated with acute conditions, however, when evaluating the composition of therapy for patients with post-traumatic disorders of the central nervous system, the leading role has been still assigned to rehabilitation and care [10]. In addition to a fairly long rehabilitation period with a very unpredictable result, patients after a traumatic brain injury often acquire permanent disability, which has an extremely adverse effect both socially and economically. This problem can be partly solved by the inhalation of an anesthetic agent - xenon, since it is an inert gas and its use is limited by a very narrow range of contraindications, namely: individual hypersensitivity to xenon, which is extremely rare, and technical limitations - the need for a high concentration of oxygen in the inhaled mixture, and the use of semi-open or semi-closed circuits without capture units. Intactness in relation to homeostasis of patients in severe and extremely serious condition, the absence of accumulation effects, the relative ease of use, as well as the rapid onset and termination of its action, represent an additional value of this drug. In our work, we tried to evaluate the effect of xenon on the processes of neurogenesis by assessing the dynamics of neuroinflammation markers and regeneration of nervous tissue. A certain trend towards a decrease in the levels of interleukin-6 and α-1 acid glycoprotein in the blood may indicate that the scheme used by us is able to influence the processes of chronic inflammation. However, the method of xenon administration (concentration, exposure, frequency or duration) needs to be adjusted to achieve a better result. Also, a positive effect on BDNF levels suggests a "start" of the processes of nervous tissue restoration, which at this stage can help improve the rehabilitation potential of the patients and reduce the severity of neurological deficit in the future. The fact that the S100 b level remains within reference values throughout the course of therapy, including its determination before the start of inhalation, casts doubt on the significance of assessing its level for judging the effectiveness of the therapy.

FINDINGS

1. Inhalations of the oxygen-xenon gas mixture for 7 days did not have a statistically significant effect on the parameters of neuroinflammation (interleukin-6, α-1 acid glycoprotein), however, in this category of patients, there was a certain trend towards a decrease in the level of these indicators in the blood (p=0.07 in the case of interleukin-6 and p=0.09 in the case of α-1 acid glycoprotein).
2. Inhalations of the oxygen-xenon gas mixture for 7 days led to a statistically significant increase in the concentration of BDNF in the blood compared to the Comparison group (p=0.04).
3. Determination of the dynamics of the S100 b protein does not carry prognostic significance in the described scheme of xenon inhalation for this category of patients.

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