Research Article

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A New Strategy for the Treatment of Patients With Prolonged Impairment of Consciousness Using Xenon. Prospective Pilot Study

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ABSTRACT In addition to high mortality, craniocerebral injuries have another danger, a long rehabilitation period and a high percentage of disability with the development of cognitive impairment. This is primarily associated with the processes of neuroinflammation, which development, according to recent data, leads to a long-term impairment of consciousness. The anti-inflammatory effects of xenon inhalation anesthetic, which have been repeatedly shown in previous studies, have the potential to beneficially affect the level of consciousness in these patients by targeting key links of neuroinflammation.

AIM OF STUDY To evaluate the effect of oxygen-xenon mixture inhalation on the level of consciousness recovery and the severity of spastic activity in patients after traumatic brain injury.

MATERIAL AND METHODS A prospective randomized clinical trial of the effect of inhaled xenon sedation on the level of consciousness and spastic activity in patients with post-coma long-term impairment of consciousness was conducted. Patients were randomized into two equal groups. In group I (comparisons, n=15) (in addition to the standard treatment after a traumatic brain injury), each patient included in the study 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 (study, n=15) (in addition to standard treatment), each patient included in the study inhaled an oxygen-xenon gas mixture (xenon content 30 vol%) for 7 days 1 time per day. Before and after the course of treatment (on the 7th day), patients were assessed using the CRS-R scale and the modified Ashworth scale.

RESULTS The final evaluation included 12 patients from the comparison group and 12 patients from the study group. Three patients were excluded from each group as a result of critical incidents not related to the type of the therapy. In the comparison group on the 7th day, the level of consciousness was score 9 [7; 11] and did not differ statistically significantly from the baseline ($p>0.05$), which was score 8 [6; 10]. Spastic activity also did not change statistically significantly. In group II, the initial level of consciousness was 9 [7; 10], and on the 7th day — score 15 [12; 17], which was statistically significantly higher both in relation to the level of consciousness by the 1st day ($p=0.021$) within the group, and in relation to it on the 7th day in group I ($p=0.038$). When comparing spastic activity on the 1st and 7th days, we did not obtain a statistically significant difference in any of the groups.

CONCLUSION Our method of xenon inhalation made it possible to have a beneficial effect on the level of consciousness of patients after traumatic brain injury, but this did not affect the final level of spastic activity in any way.

Key words: xenon, traumatic brain injury, impaired consciousness, neuroinflammation, neuroprotection, rehabilitation

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BACKGROUND

The problem of long-term impairment of consciousness after traumatic brain injury (TBI) doesn't lose relevance over time, and also gradually comes to the fore. This is mainly associated with an increase in the incidence of severe concomitant injury, whereTBI occurs in about a third of cases [1–3]. In turn, a long-term impairment of consciousness contributes to the development of secondary complications that significantly worsen the prognosis in this category of patients [4]. Within the framework of modern ideas about the causes and pathogenesis of a long-term impairment of consciousness, the process of neuroinflammation is of the greatest interest [5]. If primary injuries as a result of the injury itself predominate in the acute period, then in a few days, inflammatory processes begin to come to the fore, leading to undesirable consequences in the form of cognitive impairment and prolonged impairment of consciousness [6].

The search for a drug that can at least significantly minimize the consequences of TBI, has been going on for a long time. Understanding the root causes, as well as pathological cascades and main targets within neuroinflammation, suggested that the effects of the inhaled anesthetic xenon could potentially have a beneficial effect on the recovery of this group of patients [7–9]. In a previous experimental study, we proved a clear anti-inflammatory effect of this anesthetic, which was an increase in the ability of neutrophils to spontaneous apoptosis after modeling an inflammatory response [10]. This effect was realized by reducing the expression of adhesion molecules *CD* 11 *b* and *CD* 66 *b* on the surface of neutrophils. Also, as a result of xenon exposure after TBI modeling *in vivo,* we proved a statistically significant decrease in the activation of pro-inflammatory genes *NF-kB* 1 and *NF-kB* 2 responsible for the synthesis of cytokines and other molecules involved in inflammation [11].

However, if a small, but still significant experience has been accumulated regarding the beneficial effect of xenon in acute conditions [12–14], then xenon was not used in patients with a long-term impairment of consciousness. At the same time, the effects of inert gases are becoming the object of more and more careful study, which ultimately can lead to a significant expansion of indications for their use [15].

Based on the understanding of the complex effect of xenon on neuroprotection, we conducted a pilot randomized controlled trial, the purpose of which was to study the effect of this anesthetic on the rehabilitation potential and level of consciousness of patients with severe neurological deficits and long-term impairment of consciousness as a result of TBI.

Aim of study: to study the effect of inhalation of an oxygen-xenon mixture on the level of recovery of consciousness and the severity of spastic activity in patients after TBI.

MATERIAL AND METHODS

A prospective randomized clinical trial of the effect of inhaled xenon sedation on the level of consciousness in patients with post-coma long-term impairment of consciousness was presented. The study was conducted within the framework of the current topic of the state assignment No. 075-01414-20-02 "Anesthetic neuroprotection with xenon and sevoflurane in severe brain damage. Clinical-experimental study" and was approved by the local ethical committee (minutes of the meeting of the ethical committee 4/21/2 dated 29.09.21, No. 427/04.10.2021). Patients were divided into two groups equal in number of participants (Fig. 1). In group I (comparisons, n = 15), patients received standard treatment within the framework of the current protocols for providing care for long-term impairment of consciousness as a result of 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 (studies, n = 15), patients also received standard treatment, however, inhalation with an oxygen-xenon mixture (xenon content - 30 vol%) was additionally carried out for 7 days, 1 time per day. After the course of treatment, the level of consciousness and spastic activity was assessed using the revised *CRS-R* coma recovery scale and the modified Ashworth scale.

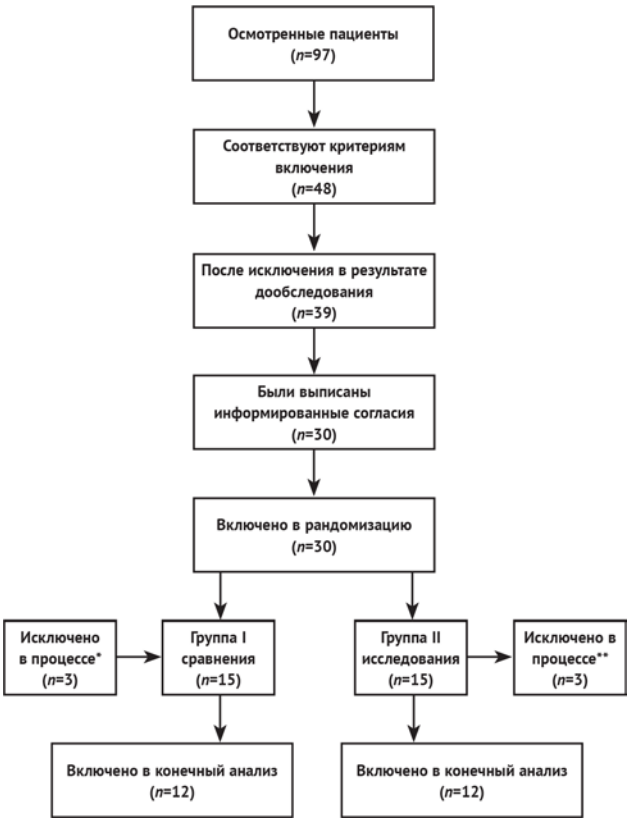

Fig. 1. Flow chart of inclusion and exclusion from the study.
Note: * - in one case, emergency surgical treatment of gastrointestinal bleeding was required, in two cases, there was a need for artificial lung ventilation; ** - in two cases, inotropic support was required, in one case, it became necessary to perform a bypass operation due to an increase in intracranial hypertension

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

Inclusion Criteria:

- men and women aged 18 to 65;
- patients with severe brain damage due to traumatic brain injury;
- level of consciousness: vegetative state or a state of minimal consciousness;
- independent breathing;
- informed consent of the patient or his legal representative to participate in a scientific study.

Exclusion Criteria:

- presence of indications for emergency surgical intervention;
- the need for inotropic and vasopressor support, assessed as *VIS score* 10 and higher;
- aggravated allergic history;
- drug intolerance;
- the investigator may decide to early terminate the patient's participation in the study at any time if the patient's condition requires it.

To eliminate the preferences of the researchers, the recruitment into groups was carried out by the envelope method.

After the start of the study, 3 patients were excluded from group I (comparison): in one case, emergency surgical treatment of gastrointestinal bleeding was required, and in two cases, mechanical ventilation was necessary. Three patients were also excluded from group II (study): in two cases, inotropic support was required, in one case, it became necessary to perform a bypass operation due to an increase in intracranial hypertension. The age composition and sex of patients included in the study are presented in Table 1.

As can be seen in Table 1, the groups were comparable in terms of mean age, comorbid background, and methods of standard therapy used.

Table 1

Composition of the comparison and study groups

Comparison group, mean age 31.4±11.5 years			
Age of patients	Men	Women	Total
18–30 years old	3	2	5
31–40 years old	1	2	3
41–50 years old	3	1	4
Total	7	5	12
Study group, mean age 32.5±12.5 years			
Age of patients	Men	Women	Total
18–30 years old	4	1	5
31–40 years old	3	2	5
41–50 years old	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 KTK-01 xenon therapeutic circuit (Akela-N, Russia) (Fig. 2) was used, equipped with an oxygen and xenon gas analyzer, as well as a xenon dispenser that allows you to control both the current consumption and the total consumption. All patients included in the study were on their own breathing through a tracheostomy tube. Before the procedure, the patient's tracheostomy tube was sanitized and the cuff was inflated to further seal the breathing circuit and minimize xenon loss during inhalation.

Fig. 2. Xenon therapeutic circuit KTK-01, designed to supply a respiratory mixture using oxygen, xenon, or a combination of these gases

In group I (comparison), inhalation with an oxygen-air mixture was carried out according to the following method: after the patient was connected to the xenon therapeutic circuit, a five-minute denitrogenization was performed by inhalation with 100% oxygen until a stable oxygen concentration in the circuit was 95–97% vol. 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 with an oxygen-air mixture while maintaining a constant oxygen concentration of 30 vol%. During the procedure, the electrocardiogram was monitored in three leads with the calculation of heart rate and blood pressure by a non-invasive method, as well as plethysmography with pulse oximetry. After 30 minutes, the therapy circuit was disconnected and the procedure ended.

In group II (studies), denitrogenation was performed according to the same method, however, after that, immediately after the exhalation valve was closed, xenon was fed into the circuit at a rate of 0.5–1 l/min until a concentration of 30 vol.% was reached. Further, the specified concentration was maintained for 30 minutes with monitoring similar to 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 0 vol%, after which the patient was disconnected from the circuit.

Before and after the completion of the course, the following indicators were assessed:

1. The level of recovery after coma using the *CRS-R scale* (*Coma Recovery Scale-Revised*) [16].
2. The severity of spastic activity using the modified Ashworth scale [17].

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

RESULTS

When assessing the level of recovery of consciousness in the comparison group, we did not obtain statistically significant ($p > 0.05$) differences between the initial and final points (Table 2). The initial value was 8 [6; 10] points, the final value was 9 [7; 11].

In group I (comparison), there were also no statistically significant ($p > 0.05$) differences in assessing spastic activity (Table 3). Before the procedures, it was 3 [1; 3] points, and upon completion it was 2 [1; 3].

Table 2

Dynamics of recovery of consciousness in the study group

Patient code, age	Diagnosis	Level of consciousness (*CRS-R*), points	
		Before the course	After the course
1, 22	TBI	VS, 5	VS, 5
2, 20	TBI	SMC, 6	SMC, 6
3, 38	TBI	SMC, 7	SMC, 7
4, 33	TBI	SMC, 7	SMC, 7
5, 26	TBI	VS, 6	VS, 6
6, 35	TBI	SMC, 9	SMC, 9
7, 45	TBI	SMC, 10	SMC, 12
8, 21	TBI	VS, 8	VS, 8
9, 29	TBI	SMC, 9	SMC, 9
10, 32	TBI	SMC, 13	SMC, 16
11, 19	TBI	SMC, 6	SMC, 9
12, 38	TBI	SMC, 8	SMC, 9

Notes: VS - vegetative state; SMS - state of minimal consciousness; TBI - traumatic brain injury

Table 3

Change in spastic activity in the comparison group

Patient code, age	Diagnosis	Modified Ashworth scale, points	
		Before the course	After the course
1, 22	TBI	1	1
2, 20	TBI	3	1
3, 38	TBI	2	2
4, 33	TBI	3	2
5, 26	TBI	1	1
6, 35	TBI	2	2
7, 45	TBI	3	2
8, 21	TBI	1	1
9, 29	TBI	1	1
10, 32	TBI	2	2
11, 19	TBI	3	2
12, 38	TBI	3	1

Note: TBI — traumatic brain injury

In group II (research) on the 7th day there was a statistically significant (p = 0.021) improvement in the level of consciousness in relation to the initial one. At the start of the study, the score was 9 [7; 10], and after the course of treatment it was 15 [12; 17] (Table 4). It should be also noted that in the intergroup comparison of the results on the 7th day, the level of consciousness in group II (research) was statistically significantly (p = 0.038) higher than in group I (comparison).

Table 4

Level of consciousness before and after xenon therapy

No.	Patient code, gender, age	Diagnosis	Level of consciousness (*CRS-R*), points	
			Before the course	After the course
1	M1, 38	TBI	SMC, 12	SMC, 14
2	M2, 45	TBI	SMC, 7	SMC, 7
3	M4, 22	TBI	SMC, 13	Conscious, 23
4	Zh1, 39	TBI	SMC, 5	SMC, 18
5	Zh2, 28	TBI	SMC, 10	Conscious, 23
6	Zh3, 37	TBI	SMC, 8	SMC, 13
7	M5, 28	TBI	VS, 5	SMC, 11
8	M6, 20	TBI	VS, 9	SMC, 16
9	M7, 44	TBI	SMC, 7	SMC, 10
10	M8, 38	TBI	VS, 4	VS, 7
11	M9, 25	TBI	SMC, 13	SMC, 18
12	J5, 29	TBI	SMC, 13	SMC, 18

Notes: VS - vegetative state; SMS - state of minimal consciousness; TBI - traumatic brain injury

When determining spastic activity, we did not obtain a statistically significant difference (p >0.05) on the 7th day in relation to the initial level (Table 5). During the procedure, there was a decrease in its definition, but after the end, after some time, the muscle tone returned to its original level.

Table 5

Initial and final level of spasticity in group II

No.	Patient code, gender, age	Diagnosis	Modified Ashworth score	
			To the course	After the course
1	M1, 38	TBI	2	2
2	M2, 45	TBI	1	3
3	M4, 22	TBI	3	1
4	Zh1, 39	TBI	1	2
5	Zh2, 28	TBI	2	1
6	Zh3, 37	TBI	2	1
7	M5, 28	TBI	2	2
8	M6, 20	TBI	1	1
9	M7, 44	TBI	1	0
10	M8, 38	TBI	3	2
11	M9, 25	TBI	1	0
12	Zh5, 29	TBI	1	1

Notes: TBI — traumatic brain injury

CONCLUSION

Organoprotection by inert gases is becoming the subject of more and more careful study [18]. This is partly associated with their intactness with respect to enzyme systems and excretion from the body in an unchanged state, which potentially facilitates their use in patients in extremely severe conditions. A 2019 research paper [19] compared the neuroprotective potential of all inert gases in a model of ischemic brain injury. The highest potential was noted for xenon and argon, while the remaining gases (krypton, neon and helium) did not have a significant effect on the severity of hypoxic damage. Later, in a large meta-analysis in 2021, previously available data were summarized and a conclusion was made about the unequivocal effectiveness of xenon in brain damage of various origins [20]. This work included a number of large experimental studies aimed at determining the mechanisms of neuroprotection implementation and possible schemes of use [21, 22]. However, among the previously performed works, there is not one that would evaluate the effects of xenon in patients with a long-term impairment of consciousness.

The technique we used made it possible to statistically significantly affect the recovery of the level of consciousness in this category of patients, which, in turn, contributed to an improvement in the prognosis. Despite the fact that not all of the patients who participated in the study were able to demonstrate a significant improvement in their condition, after 7 days the results in the study group were statistically significantly better than in the comparison group. It is also worth noting that in group II (study) on the 7th day, two patients regained a clear consciousness (though with persistent cognitive impairment), which was not observed in group I (comparison). The data obtained are unique, first of all, in that the current treatment protocols for this category of patients are not able to significantly affect the level of consciousness [4].

The results of the pilot stage of the study allow us to hope that the anti-inflammatory effects of xenon will contribute to the resolution of pathological processes leading to a long-term impairment of consciousness. A small sample does not allow us to draw unambiguous conclusions about the prospects of this therapy, but we hope to get answers to all our questions in the course of further research.

Also, the question remains open regarding spastic activity, which high level of which negatively affects the condition of patients. It is possible that the absence of a significant result is a consequence of the insufficient duration of the procedure, however, only further study of the non-anesthetic effects of xenon will help to draw unambiguous conclusions. In addition, earlier data were obtained on a significant decrease in spastic activity in children with neonatal hypoxic-ischemic encephalopathy [23–25].

1. Oxygen-xenon gas mixture inhalations for 7 days made it possible to statistically significantly improve the indicators of the level of consciousness relative to the initial one in patients after traumatic brain injury ($p = 0.021$).

2. The use of xenon contributed to better recovery of consciousness, assessed on the 7th day, compared with the indicators in the comparison group for the same period ($p = 0.038$).

3. The use of xenon did not have a statistically significant effect on the severity of spastic activity, except for the period of the procedure ($p > 0.05$).

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