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Hyperbaric oxygenation therapy in treatment of traumatic spinal cord injury: a pilot study

Oleksii S. Nekhlopochyn[1], Igor V. Voronov[2], Vadim V. Verbov[3]

[1]Spine Surgery Department, Romodanov Neurosurgery Institute, Kyiv, Ukraine
[2]Department of Hyperbaric Oxygenation, Romodanov Neurosurgery Institute, Kyiv, Ukraine
[3]Restorative Neurosurgery Department, Romodanov Neurosurgery Institute, Kyiv, Ukraine

Address for correspondence:
Oleksii S. Nekhlopochyn, Spine Surgery Department, Romodanov Neurosurgery Institute, 32 Platona Maiborody st., Kyiv, 04050, Ukraine, e-mail: AlexeyNS@gmail.com

Spinal cord traumatic injury as resulting persistent movement and sensory disorders is one of the most disabling consequences of traumatic factor impact on the human body. Despite a large number of experimental and clinical studies aimed at developing methods for restoring lost functions, there is no acceptable solution to the problem. One of the promising areas in the treatment and rehabilitation of this category of patients is the use of hyperbaric oxygenation (HBO). Experimental models have shown that HBO has a neuroprotective effect in spinal cord injury, but the results of clinical application of the method are still controversial.

Objective: to determine the effectiveness of HBO in the complex therapy of victims with traumatic spinal cord injury and the feasibility of further study of this area.

Materials and Methods: Study design is a pilot observational retrospective "case – control". The database of patients with spinal cord injury who were hospitalized at Romodanov Neurosurgery Institute in the period from 2010 to 2020 were used for the analysis. When selecting a control for each clinical case, the following factors were considered: gender, age, circumstances of injury, type of damage to the osteoligamentous apparatus, level of neurological deficit, degree of damage and compression of the spinal cord, time elapsed from the moment of injury to surgery. 28 "case – control" pairs were analyzed. The main criterion for therapy effectiveness was the change in the functional class according to the ASIA scale.

Results. Positive dynamics was registered in 57% of victims, including in the group of patients receiving HBO therapy - in 71%, in the control group - in 43%. HBO therapy in the postoperative period significantly affects the dynamics of regression of neurological disorders (p=0.0295). The odds ratio is 3.333 (95% confidence interval - 1.098–10.116, p=0.0335). The calculation of the odds ratio, adjusted for additional analyzed factors, showed a more pronounced efficiency - 4.519 (95% confidence interval - 1.279–15.962, p=0.0192).

Conclusions. The obtained results indicate that usage of HBO as a method of complex therapy for traumatic spinal cord injury is promising for further study in order to determine the effectiveness of the method, the optimal timing of treatment initiation in the postoperative period and its duration.

Keywords: *traumatic spinal cord injury; hyperbaric oxygenation; neurological deficit*

Introduction

Traumatic spinal cord injury (SCI), which is often accompanied by permanent motor and sensory disorders, has a major impact on the quality of life of patients and always has certain socio-economic consequences for both patients and their families. The main reason for the significance of the problem is the lack of effective therapy. Despite a large number of experimental and clinical studies aimed at developing methods for restoring lost functions in patients with traumatic SC injury, there is no acceptable solution to the problem. In recent decades, a large number of studies have been published that demonstrate the effectiveness of various strategic approaches in modeling spinal cord injury (SCI) in animals, but most of them are ineffective in clinical use.

Currently, the main strategic areas in the treatment of SCI are pharmacotherapy, the use of neurotrophic factors and physiotherapy methods. The main disadvantages of methods that are being tested or used in clinical practice are low efficiency, high cost, significant side effects, high complication rate, small therapeutic window. One of the strategic pathways in the treatment and rehabilitation of patients with SCI is the use of hyperbaric oxygenation (HBO).

The HBO method has a long history of clinical use. At different stages of medicine development, the attitude to the method was ambiguous. For the first time,

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compressed air for hyperbaric therapy was used in 1662 by the British physician Genshaw.

In 1775, Joseph Priestley discovered oxygen, and in 1789 Lavoisier and Seguin reported its indefinite toxic effects on the central nervous system, described in more detail in 1878 by Paul Bert, which called into question the feasibility of using HBO. However, gradually collected clinical material, contributed to the development of the technique. In 1860, the first pressure chamber was built in Canada. In fact, hyperbaric medicine was actively developed after the successful treatment in 1937 by Albert Benke of air decompression illness with the use of oxygen under high pressure. Currently, the HBO method is used to treat a wide range of pathological conditions (poisoning, including carbon monoxide, infectious diseases, injuries), in the complex therapy of healing large wound processes and more.

Experimental models have shown that HBO has a neuroprotective effect in SCI, traumatic brain injury (TBI), neurodegenerative diseases, peripheral nerve damage and neurotoxic effects. The main mechanisms causing a positive effect are antioxidant, anti-inflammatory, anti-apoptotic properties, as well as improving the oxygen supply to the nervous tissue. However, the question of the expediency of clinical use of HBO in the treatment of SCI has been little studied, and the research results presented in the publications are controversial.

Objective: to determine the effectiveness of hyperbaric oxygenation in the complex therapy of patients with traumatic spinal cord injury and the feasibility of further study in this area.

Materials and methods

Study design: pilot observational retrospective "case-control".

Study participants: a database of patients who were hospitalized at Romodanov Neurosurgery Institute, Ukraine in the period from 2010 to 2020 with SCI. Patients underwent surgery of the required volume depending on the nature of the injury and the degree of compression of the SC.

All patients signed an informed consent for the processing of treatment outcomes while maintaining confidentiality. The study was approved by the Commission on Ethics and Bioethics of the Institute of Neurosurgery named after Acad. A.P. Romodanov, Ukraine (Minutes No.4 of September 5, 2018). The work is a fragment of research work (state registration number 0119U000110).

Inclusion criteria:

• isolated SCI at the level of the cervical (subaxial level) and thoracic or thoracolumbar transition;

• compressive nature of SC injury;

• age of patients 18-60 years;

• availability of a documented in details dynamics of changes in neurological status;

• neurological deficit at the time of hospitalization, corresponding to the functional class B – D according to the ASIA scale (American Spinal Injury Association) [1];

• availability of informed patient consent.

Exclusion criteria

• the presence of compression of the structures of the spinal canal in the postoperative period, kyphotic deformation of the operated spinal motion segment, failure of stabilization or other signs of ineffective surgery;

• topical mismatch of the injury level to the clinical pattern or deepening of the neurological deficit in dynamics;

• the presence of postoperative infectious and inflammatory complications;

• the presence of a neurological deficit of any etiology and severity before the injury (as a result of previous traumatic brain injury (TBI), demyelinating processes in the central nervous system, damage to peripheral nerves, etc.);

• a history of injuries and / or surgery on the spine or neck prior to the injury analyzed in this study;

• the presence of injuries in the history and / or instrumentally confirmed inflammatory or clinically significant degenerative-dystrophic changes of any part of the spine;

• the presence of a neoplastic process of any localization or any somatic pathology in the stage of decompensation;

• the presence of persistent mental and behavioral disorders.

The study did not involve patients with a level of neurological disorders corresponding to ASIA A functional class, since such a neurological deficit does not fully characterize the degree of morphological changes in the SC. Both the severe contusion and the spinal cord laceration may be characterized by an identical clinical pattern, but the time course of recovery may differ significantly.

The following characteristics were analyzed: gender, age, mechanism of injury, duration of the period from the moment of injury to surgery. Based on the data of preoperative computed tomography and magnetic resonance imaging, the level of injury and the nature of osteo-traumatic changes were determined according to AOSpine subaxial cervical spine classification system or AOSpine Thoracolumbar Spine Injury Classification System [2,3]. The functional class of neurological disorders was established according to the ASIA scale upon admission to the hospital and at discharge. The severity of SC injury was assessed using The Brain and Spinal Injury Center score (BASIC scale) [4]. The degree of SC compression in the preoperative period was determined by calculating the compression factor [5].

The criterion for the effectiveness of therapy was the reduction of neurological disorders (change in the ASIA functional class).

The technique of performing hyperbaric oxygenation

Sessions were carried out in single pressure chambers "OKA-MT" and "Yenisei-3". In the first session, an overpressure of 0.2 ATA was created for 30 min, in subsequent sessions - 1.8–2.0 ATA for 60–70 min. The average number of sessions per course is 10-12.

Statistical processing

This article contains some figures that are displayed in color online but in black and white in the print edition

Statistical data processing was performed using R (version 4.0.5., R Foundation for Statistical Computing) in the RStudio development environment (version 1.4.1106). In the analysis, the probability of statistical error of the first kind was taken as α = 0.05, errors of the second kind - as β = 0.2. The compliance assessment of the trait to the normal distribution law was assessed using the Shapiro-Wilk test, and assessment of the homogeneity of the groups by nominative traits was assessed using Pearson's chi-square test or Fisher's exact test. To determine the degree of influence of individual parameters on the outcome of therapy, analysis of variance was performed. The odds ratio (OR) was defined as the exponent of the coefficients of the logistic regression model. The quality assessment of the binary envisioned ability classification was performed by constructing the ROC curve and determining the area under the curve.

Data are given as median and 95% confidence interval.

Results

General characteristics of patients

The analysis of case histories revealed 43 patients who were eligible to take part in this study. As a result of further processing, 12 cases were excluded for the following reasons: an increase in neurological symptoms (n = 2), cerebrospinal fluid (n = 1), previous spinal surgery (n = 1), the history of trauma (n = 2), insufficient number of clinical data (n = 6). Thus, data from 31 patients were used for the final analysis.

Taking into account the large number of factors that determine the time course of regression, the following assumptions were used when selecting control for each clinical case:

- gender - full compliance;
- age - the difference is not more than 5 years;
- circumstances of the injury - full compliance for diver's injuries, in other cases - partial;
- type of damage - compliance with the main classes of AOSpine classifications;
- neurological deficit - compliance within the ASIA functional classes;
- the nature of the damage to the SC - the difference is not more than 1 class according to the BASIC scale (if possible, assessment);
- degree of SC compression - the difference is not more than 2 mm;
- time from the moment of injury to surgery:

up to 24 hours - the difference is not more than 2 hours;

from 1 to 3 days - the difference is not more than 6 hours;

more than 3 days - the difference is not more than 2 days.

Despite the presence of a large base of patients, no control pair was found for 3 clinical cases. Thus, further 28 case-control pairs were analyzed ***(Table 1).***

Efficacy evaluation of therapy

When analyzing the results of therapy it was revealed that the positive time course according to our chosen assessment criterion was registered in 57% of patients, in particular, in 71% in the group of patients receiving HBO therapy and in 43% in the control group.

According to the results of assessing the influence of additional factors, the time course of regression of neurological disorders is statistically most significantly influenced by the degree of compression of SC (p = 0.025) and the period from the moment of injury to surgery (p = 0.032), is moderately - the degree of SC injury (p = 0.049) and morphological type of fracture (p = 0,051). The gender of the patient and circumstances of the injury do not significantly affect the therapy efficacy (p = 0.809 and p = 0.268, respectively).

It was found that HBO therapy in the postoperative period significantly affects the time course of regression of neurological disorders (p = 0.0295): OR - 3,333 (95% confidence interval - 1,098–10,116, p = 0,0335). Calculation of OR, adjusted for the degree of compression of SC, the time that elapsed from injury to surgery, the degree of SC injury according to magnetic resonance imaging and morphological type of damage to the spinal motion segment, demonstrated a more pronounced efficiency - 4,519 (95% confidence interval – 1,279–15,962, p=0,0192).

The data presented indicate that the model used in the calculations is quite effective (the area under the ROC-curve is 0.74) and, despite the small sample used in its construction, has sufficient predictive capability for a binary feature. Accordingly, the results obtained indicate a significant impact of the studied method on the outcomes of treatment.

Discussion

It is known that in pathophysiological processes that cause traumatic SC injury, primary and secondary damage can be distinguished [6]. Primarily SC is injured directly as a result of mechanical action, while the secondary damage is delayed and is characterized by a complex cascade of pathophysiological processes (oxidative stress, ischemia, edema, inflammation, excitotoxicity and apoptosis) [7,8]. Since the primary damage is most often irreversible, the main therapeutic methods for improving the neurological status of victims are aimed precisely at the mechanisms of secondary damage [9].

An example of one of the most common methods of preventing secondary damage to the SC is the use of methylprednisolone in the most acute (first 8 hours) period of injury [10]. In this aspect, the study conducted by S. Kahraman et al. is of considerable interest [11]. The authors simulated SC compression in mice and compared the effectiveness of therapy with HBO or methylprednisolone. It was found that it was HBO, rather than steroid pharmacotherapy, reduced the content of superoxide dismutase and glutathione peroxidase in the SC tissue, which indicates a greater influence on oxidative stress processes. The clinical advantage of HBO over steroids was demonstrated by J.D. Yeo et al. [12] when simulating the contusion damage of SC in sheep.

Obviously, the availability of oxygen plays an integral role in the cell survival in traumatic SC injury. Additionally, a number of experimental studies have identified other potential mechanisms of the neuroprotective effect of HBO [13,14]: 1) inhibition of apoptosis, 2) reduction of oxidative stress, 3) reduction of inflammation, 4) stimulation of angiogenesis, 5) reduction of spinal cord edema, 6) enhancement of autophagy, etc.

Table 1. General characteristics of patient groups

Indicator	The group that received the HBO course (n=28)	Control group (n=28)	P
Gender:			
males	18	18	1*
females	10	10	
Age, years	36,0 (32,29–40,99)	31,5 (29,96–39,9)	0,588**
Injury level:			
cervical spine	12	12	1*
thoracic section	5	5	
thoracolumbar transition	11	11	
Circumstances of injury:			
road traffic incident	10	10	0,923***
diving	9	9	
fall from a height	4	3	
fall on a plane	4	3	
other	1	3	
Type of injury (according to AOSpine):			
A	7	7	1*
B	13	13	
C	8	8	
Functional class ASIA:			
B	10	10	1*
C	11	11	
D	7	7	
The degree of damage to the SC:			
Basic 0	5	6	0,848*
Basic 1	11	9	
Basic 2	12	13	
SC compression, mm	6,0 (5,41–6,34)	5,5 (5,39–6,29)	0,759**
Time from injury to surgery:			
<24 hours, hr	17,5 (10,97–22,36)	18,0 (11,47–22,2)	0,872**
1–3 days, hr	49,0 (35,06–57,94)	47,5 (36,85–55,65)	0,771**
>3 days, day	5,5 (4,75–6,25)	5,0 (4,74–5,92)	0,745**
Time from surgery to the beginning of the HBO course, days	4,0 (3,69–4,81)	–	–

Notes: * - χ2; ** - asymptotic Wilcoxon – Mann – Whitney test; *** - Fisher's exact test.

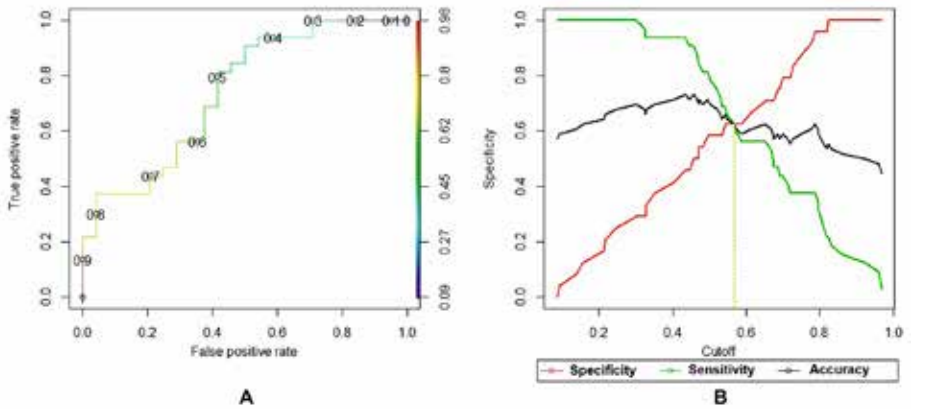

Fig. 1. Graphic characteristic of the predictive efficiency of the model: A - ROC-curve; B - the ratio of sensitivity and specificity of the model, determination of the cut-off level

Apoptosis is a form of programmed cell death, that is observed in various diseases and pathological conditions, in particular in traumatic injuries of the SC. Apoptotic cells are found peripherally of the lesion and in the adjacent white matter, mainly in the ascending pathways, within a few months after injury [15]. Therefore, according to some authors, apoptosis is a promising target of therapeutic effects in traumatic SC injury. Currently, a large number of both inducers and markers of programmed cell death are known.

It is known that after exposure to a traumatic agent on SC, the transcription of nuclear factor-κB (NF-κB) activates many pro-inflammatory genes, in particular inducible nitric oxide synthase (iNOS). The latter catalyzes the synthesis of nitric oxide (NO) - a key inflammatory mediator that activates apoptosis [16]. Y. Yu et al. [17], using a contusion model of SC trauma in rats, demonstrated that early HBO reduces the iNOS gene expression and thus prevents the development of apoptosis.

Inflammatory cytokines, interleukin (IL) -1β and tumor necrosis factor (TNF) -α are known mediators of nerve tissue apoptosis [18]. Modeling SC compression in rats R.A. Tai et al. [19] registered a significant decrease in overproduction of IL-1β and TNF-α after HBO compared with the control group.

Other studies have demonstrated a decrease in the expression of apoptosis-associated Speck-like protein (ASC), the level of CCAAT-enhancer-binding protein and an increase in the content of mitochondrial protein Bcl-2 in traumatic SC injury under the influence of HBO therapy, which also indicates the effect of inhibiting apoptosis. [20,22].

One of the basic mechanisms of secondary SC injury in traumatic exposure is the formation of free radicals [23]. The central nervous system is particularly susceptible to oxidative stress due to its high lipid content, therefore lipid peroxidation (LPO), as noted above, is a popular target of pharmacological action [13,24]. A number of studies have found the ability of HBO to reduce the manifestations of oxidative stress. Thus, H. Nie et al. [25], studying the content of malondialdehyde - a marker of LPO in the central nervous system, in ischemia-reperfusion of SC in rabbits noted that HBO once a day for 5 days contributed to a significant reduction of malondialdehyde level. The biochemical parameters correlated with the time course of recovery of motor functions.

HBO has been shown to promote activation of antioxidant enzymes in traumatic SC injury. K. Topuz et al. [26] using a compression model of SC injury in rats recorded an increase in the activity of glutathione peroxidase, superoxide dismutase and catalase after the course of HBO therapy compared with the control group. The authors also noted a correlation between clinical and biochemical values.

Q. Li et al. [27] found in vitro studies that HBO stimulates the expression of mRNA hemoxygenase - an enzyme that catalyzes the breakdown of heme to carbon monoxide, iron and biliverdin with the formation of bilirubin as a result of further reduction of biliverdin. It is known that carbon monoxide, biliverdin and bilirubin have antioxidant properties and, accordingly, a neuroprotective effect [28]. In addition, other biomechanical mechanisms have been found that determine the positive effect of HBO on the regulation of LPO [29,30].

A number of studies have demonstrated a significant effect of HBO on the inflammatory processes accompanying traumatic SC injury. Thus, it is shown that the use of HBO in experimental animals after modeling the traumatic effect is accompanied by a decrease in proinflammatory cytokines level (IL-1β and TNF-α) and myeloperoxidase - an indicator of neutrophil infiltration, and contributes to an increase of the content of anti-inflammatory cytokine IL-10 [19].

C.K. Geng et al. [31] when studying the macrophage response that occurs after SC injury, noted a change in the polarization of macrophages while using HBO therapy. The authors recorded an increase in the level of alternatively activated macrophages (phenotype M2: arginase-1 or CD206-positive) and a decrease in the content of classically activated macrophages (phenotype M1: iNOS or CD16 / 32-positive). This correlated with axon preservation and increased myelin levels and, consequently, with functional recovery in the group of animals receiving HBO.

J. Yang et al. [32] observed a decrease in the level of matrix metalloproteinases-2 and 9, involved in the degradation of the extracellular matrix, when using HBO in animals with experimentally simulated SC trauma compared with the control group. In addition, a decrease in the amount of chemoattractant protein-1 monocytes (MCP-1) - chemokine, which is involved in engaging monocytes and lymphocytes into sites of inflammation was noted under the influence of HBO. This contributes to the suppression of the inflammatory response as a factor in secondary nerve tissue damage [33]. Other immunohistochemical mechanisms of suppression of the inflammatory response in SC during HBO therapy have also been described [34–36].

Experimental models of traumatic SC injury have shown the ability of HBO to stimulate angiogenesis by vascular endothelial growth factor, as well as to limit the development of edema by inhibiting the expression of aquaporins-4 and 9 [37,38].

Most of these data have been obtained in studies carried out in the last decade, which indicates a growing interest in HBO as one of the methods of therapy of traumatic SC injury. However, the clinical usage of the method is currently limited. Only a few publications are devoted to clinical studies of the effectiveness of barotherapy [39,40]. This is probably due to technical difficulties of using the method within a small therapeutic window, defined in the experimental study. It is clear that administration of HBO to a patient with traumatic SC injury during the first day and even more so during the first 6-8 hours from the moment of injury is extremely difficult, and in most cases impossible, which actually limited the study in this direction for a long time.

There is a certain discrepancy between the experimental modeling of traumatic SC injury and real clinical situations. It is known that in most cases traumatic SC injury is combined with its compression, which lasts from the moment of injury to the performance of decompression surgery, while isolated contusion injuries are rare. In the experiments the "compression – small exposure – decompression" model is usually used,

ie the effectiveness of HBO is actually assessed not only after a short period of time after injury, but also after decompression of the SC.

Currently, post-decompression changes of SC are practically not studied, but isolated publications indicate that, for example, edema is most pronounced after the elimination of mechanical compression of SC [41]. Specifically, this fact explains the possible feasibility of using the method in the early postoperative period.

Taking into account the retrospective nature of our study, a rather heterogeneous and small group of patients receiving HBO therapy, it is not possible to develop clear clinical guidelines for the use of the method in the complex therapy of patients with traumatic SC injury. However, the results convincingly suggest the need for further study in this area, since even a small additional regression of neurological deficits that can be achieved is of great importance for this category of patients.

Conclusions

The results obtained in our pilot study demonstrate that the use of hyperbaric oxygenation as a method of complex therapy of traumatic spinal cord injury is promising for further study in order to determine the true effectiveness of the method, the optimal timing of treatment initiation in the postoperative period and its duration. The use of additional instrumental and biochemical tests will allow clarifying and objectifying the clinical component of the results of further research.

Information disclosure

Conflict of interest

The authors declare no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

The informed voluntary written consent to participate in the study was obtained from each patient.

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