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The Safety of Hyperbaric Oxygen Therapy in the Treatment of Covid-19

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RELEVANCE Acute respiratory infection COVID-19 caused by the SARS-CoV-2 (2019-nCov) coronavirus is severe and extremely severe in 15—20% of cases, which is accompanied by the need for respiratory support. Hyperbaric oxygenation is recognized as an effective therapy for replenishing any form of oxygen debt.

AIM OF STUDY To study the safety of HBO use in patients with COVID-19.

MATERIAL AND METHODS We examined 32 patients with the diagnosis "Coronavirus infection caused by the virus SARS-CoV-2" (10 — moderately severe patients (CT 1–2), 22 — patients in serious condition (CT 3–4), who received course of hyperbaric oxygenation (HBO). The procedures were carried out in a Sechrist 2800 chamber (USA) at a mode of 1.4–1.6 AT for no more than 60 minutes. In total, the patients received 141 HBO sessions. Before and after each HBO session, the subjective indicators of the patient's condition were assessed and the blood oxygen saturation was measured.

RESULTS An algorithm for HBO course management was developed, which consists in using "soft" modes (up to 1.4 AT) during the first session, followed by pressure adjustment (not higher than 1.6 AT) during the course to achieve maximum therapeutic effect and comfort for the patient. Against the background of the HBO course, the patients showed an increase in blood oxygen saturation in patients in both surveyed groups, as well as positive dynamics in the form of a decrease in shortness of breath, an improvement in general well-being.

CONCLUSION The inclusion of daily sessions (at least 4) of hyperbaric oxygenation in "soft" modes (1.4–1.6 ATA) in the complex therapy for COVID-19 has shown its safety and preliminary positive effect on the subjective state of the examined patients and the dynamics of blood oxygen saturation.

Keywords: coronavirus infection, COVID-19, hyperbaric oxygenation, hypoxia, hypoxemia, respiratory support

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ATA — absolute atmosphere
HBO – hyperbaric oxygenation
ALV – artificial lung ventilation
CT – computed tomography
ILV – invasive lung ventilation
NIAV – non-invasive artificial ventilation
ECMO – extracorporeal membrane oxygenation
COVID-19 – Corona Virus Disease 2019
SARS-CoV-2 – Severe acute respiratory syndrome-related coronavirus 2
SpO2 – blood oxygen saturation

INTRODUCTION

The pandemic of the new coronavirus infection COVID-19 caused by the SARS-CoV-2 coronavirus, first recorded at the end of 2019 in the city of Wuhan (People's Republic of China), and later spreading worldwide, affected more than 15 million people [1]. A significant difficulty in treating patients was the lack of sufficient information on the pathophysiology of the infectious process and adequate methods of therapy.

One of the leading causes of complications in SARS patients, along with the development of an inadequate inflammatory response of the body [2] and dysfunction of the blood coagulation system [3], is hypoxia, and in 15–20% of cases the disease proceeds in a severe and extremely severe degree, which requires additional oxygen support [4], and in some cases normobaric oxygenation, including invasive lung ventilation (ILV), is ineffective [5].

One of the ways to eliminate hypoxia is to use the technology of extracorporeal blood oxygenation (ECMO), however, ECMO, as a rule, is used as a last resort due to a number of significant disadvantages [6].

Therefore, in a pandemic, the primary task was to search for adequate methods of oxygenation, aimed not only at eliminating hypoxia and hypoxemia, but also capable of reducing the risk of transferring a patient to invasive mechanical ventilation. A combination of these characteristics is possessed by hyperbaric oxygenation (HBO) – a method based on breathing pure oxygen under high pressure, which allows eliminate any form of oxygen debt by delivering oxygen to organs and tissues by dissolving it in the body's fluids. [7]. The list of indications for HBO is constantly expanding, in particular, the International Society of Underwater and Hyperbaric Medicine (UHMS) calls HBO a method of treatment for 14 different diseases and syndromes, including disorders of regional blood supply, soft tissue infections, tissue ischemia, etc. [8]. Hyperbaric oxygenation has all the prospects for using it in complex therapy in patients with a new coronavirus infection.

The question was raised by the safety of HBO use in patients with COVID-19, since in Russian recommendations a contraindication to the appointment of HBO is bilateral subtotal pneumonia [9], and foreign sources do not classify pneumonia as a contraindication to the appointment of HBO [10, 11]. Due to the fact the pathophysiology of COVID-19 pneumonia differs from its classical manifestation, suggestions were made about the effectiveness of HBO in this case [12, 13].

These assumptions were supported subsequently by the description of the positive results of using HBO in patients with COVID-19 [14–16].

These studies prompted the inclusion of research centers dealing with baromedicine in this issue [17–20]. The State Budgetary Healthcare Institute named after N.V. Sklifosovsky, which has extensive experience in the use of HBO in the treatment of various pathological conditions, including life-threatening ones, in the shortest possible time began research on the use of HBO in the treatment of patients with COVID-19 [21–26].

The purpose of this work was to study the safety of HBO use in the treatment of COVID-19.

MATERIAL AND METHODS

Thirty three patients with a diagnosis of Coronavirus infection caused by the SARS CoV-2 virus, who were treated at the N.V. Sklifosovsky Research Institute for Emergency Medicine in 2020 were included in the study. All patients required additional high-flow oxygen therapy or non-invasive mechanical ventilation (NIMV) sessions. The patients were divided into two groups according to the severity based on the data of computed tomography (CT) of the lungs: group 1 – patients of moderate severity (CT 1–2), group 2 – patients in serious condition (CT 3–4) (Table 1)

Table 1
Characteristics of the examined patients and parameters of HBO sessions

Parameter	Value	
	Group 1	Group 2
Number of patients, n	10	22
CT scan of the lungs:		
CT-1	1 (10.0%)	-
CT-2	9 (90.0%)	-
CT-3	-	16 (72.7%)
CT-4	-	6 (27.3%)
Age, years	63.5 [51; 74]	59 [51,75 ; 67]
Gender		
male	5 (50.0%)	10 (45.5%)
female	5 (50.0%)	12 (54.5%)
SpO2 when breathing atmospheric air before 1st session HBO,%	94 [91.25; 95	90 [88; 92.75]
Initiation of the HBO course (days from the date of admission)	3.5 [1; 4]	6 [3.25; 9.5]
Number of HBO sessions in the course	4 [3; 4]	5 [3.75; 6.25]
Dropout patients due to:		
claustrophobia	-	1 (4.5%)
ear pain	1 (10.0%)	1 (4.5%)

Notes: CT – computed tomography; HBO – hyperbaric oxygenation; SpO2 – blood oxygen saturation

From the data presented in Table 1, it can be seen that with a similar distribution by age and gender, a greater degree of lung damage corresponds to a lower level of blood oxygen saturation – 90% [88; 92.75] versus 94% [91.25; 95] at CT (3–4) and CT (1–2), respectively. Differences in the median timing of HBO onset in the groups were due to the need for non-invasive ventilation (NIV) in group 2 patients.

The procedures were carried out in a Sechrist 2800 reanimation chamber (USA) (Fig. 1) at 1.4–1.6 ATA mode for no more than 60 minutes. In total, patients received 141 HBO sessions. Blood oxygen saturation was measured before and after each session.

Statistical analysis of the data was performed using the software package Statistica 10 (StatSoft, Inc., USA). Descriptive statistics of quantitative features are presented in the form of Me [Q1; Q3]. The study groups were compared using Student's t-test and Wilcoxon's test. Differences at values $p < 0,05$ were considered statistically significant.

Fig. 1. Hyperbaric oxygenation in the Sechrist chamber (78-year-old female patient A., CT-4, prone position)

RESULTS

Due to the current lack of a regulated HBO algorithm for COVID-19, we have developed our own algorithm for the HBO course (Table 2).

Table 2

HBO mode parameters

No.	Working pressure (AT), atm	Duration, min	Number of sessions	Source
1	2.0	60	1 session / day	[14]
2	1.5	60	1 session / day (7 days)	[15]
3	2.0	90	1 session / day	[16]
4	1.45	90	1 session / day	[17]
5	2.2	60	2 sessions / day (4 days)	[18]
6	1.6-2.4	30-60	5 sessions / 7 days	[20]

Notes: ATA – absolute atmosphere; HBO – hyperbaric oxygenation

The first "test" session was carried out in the 1.4 ATA mode for 30 minutes in order to identify possible contraindications and a subjective assessment of the patient's well-being during the hyperbaric session. When contraindications were identified (claustrophobia, ear pain, etc.), the session was terminated and HBO was not prescribed to the patient in the future. In the absence of contraindications and discomfort during the hyperbaric session, subsequent sessions were carried out daily in the 1.6 ATA mode for 40–60 minutes with the possibility of adjusting the working pressure during the session based on the patient's feelings.

When assessing the subjective indicators of the patient's condition, a positive trend was noted in the form of a decrease in shortness of breath and an improvement in general well-being.

When analyzing the dynamics of CT data of the lungs against the background of HBO, in a number of cases, a decrease in the intensity of damage to the pulmonary parenchyma, a decrease in the volume of damage to the lung tissue due to regression of the "ground glass" zones and the reverse development of consolidation foci were recorded. In the 1st group, one patient (10.0%) showed a decrease in the severity of infiltrative-inflammatory changes in both lungs – from CT-2 to CT-1; but in group 2, a decrease in severity from CT-3 to CT-2 was noted in 6 patients (27.3%).

When analyzing the effect of HBO sessions on blood oxygen saturation (Table 3), positive dynamics were observed in both examined groups. The difference was that a group of patients in a serious condition required a longer continuous course of HBO. So, if in the 1st group 80% of patients required 4 sessions to complete the HBO course, then in the 2nd group most of patients (81.2%) needed 6 sessions ($p<0,05$).

Table 3

Blood oxygen saturation during the course of hyperbaric oxygenation

Session number SpO 2 ,%		1	2	3	4	5	6	7	8
Group 1	before	94 [91.3; 95]	95 [93; 98]	94 [92.8; 96.8]	95 * [94; 97]	95.5 * [94.3; 96.8]	96 * [95; 97]	-	-
	after	99 [98; 100]	100 [99; 100]	100 [98.8; 100]	100 [100; 100]	100 [100; 100]	99 [98.5; 99.5]	-	-
Group 2	before	90 § [88; 92.8]	92.5 * [87.8; 96.3]	92.5 * [90; 95.8]	94 * [90; 96.5]	94.5 * [92; 96.3]	93.5 * [93; 97]	95 * [93; 95.5]	95.5 * [94.5; 96.3]
	after	99 [97.3; 100]	98 [94.8; 100]	98 [97; 100]	99 [97; 100]	99 [97.3; 100]	99.5 [98.8; 100]	99 [98.5; 99.5]	100 [99.8; 100]

Note. * – difference from baseline in the group (Wilcoxon criterion, p <0.05), § – index difference between groups (Student's t-test, p <0.05).

DISCUSSION

The interest in the inclusion of HBO in the complex therapy of patients with COVID-19 is justified by the wide range of its effects on the body, which not only compensates for almost any form of oxygen deficiency, but also mobilizes the reactions of physiological and metabolic adaptation in various pathological processes of hypoxic and non-hypoxic genesis. [9].

HBO therapy may be effective in reducing cytokine levels in COVID-19 (TNF-ά, IL-1β, IL-6) [27–29], that is, minimizing the degree of "cytokine storm" and the severity of oxidative stress [29–31], as well as improving capillary proliferation and accelerating the inclusion of collateral blood flow [32, 33]. In addition, HBO was effective for infectious complications when other methods were ineffective [34–36]. Thus, HBO can have a positive impact on all key aspects of the development of the infectious process in COVID-19. However, this assumption requires a more detailed study.

As noted above, the lack of understanding of the impact of HBO regimen on patient safety can lead to adverse effects. So, for example, despite the information in the literature on the safety of regimens up to 2.5 ATA [5], for patients with COVID-19 it is recommended to use "soft" regimens (1.3–2.0, duration 45–90 minutes) [5]. В то же время другие 2 из 6 исследований (табл. 2) предлагают «жесткие» режимы (более 2,0 АТА) без объяснения такого подхода.

In our opinion, in conditions of insufficient information about the pathophysiological aspects of the course of the infectious process, it is necessary, first of all, to be guided by the requirements of ensuring maximum patient safety, which we adhered to when developing the HBO algorithm in COVID-19.

Termination of the HBO course in 3 patients (Table 1) was associated with the identification of contraindications (claustrophobia, ear pain), expressed in patient discomfort, but not reducing the safety of the procedure.

Clinical monitoring did not reveal any drawbacks of using this approach, since the "softness" of the regime and the provision of comfort to the patient affected the stabilization of both his psychoemotional (reduction of anxiety, increased contact) and, in turn, the general state.

Analysis of CT data of the lungs did not reveal any undesirable effects (trauma to the pulmonary parenchyma, the development of pulmonary hemorrhage), which could be a consequence of HBO. Thus, the modes we use (no more than 1.6 ATA) are safe.

The main expected therapeutic effect of HBO was an increase in blood oxygen saturation. Despite the fact that after a session of blood oxygen saturation within 30 minutes it decreased almost to the initial values, there was a constant positive dynamics of this indicator from session to session (Table 3). This circumstance may be associated with the possible deposition of a certain amount of oxygen in the tissues of the body [9].

The positive dynamics of blood oxygen saturation also favorably affected the need for additional oxygen therapy. In the group of patients of moderate severity, already during the course of HBO, 70% of patients were transferred to spontaneous breathing, the remaining 30% switched to spontaneous breathing within 1–2 days after the end of the course. In group 2, refusal of additional oxygen therapy during the HBO course was observed in 31.8% of patients, another 40.9% of them switched to spontaneous breathing within 1–2 days after completing the HBO course. The remaining patients took a longer time to withdraw from supplemental oxygen therapy. At the same time, none of the patients from both examined groups required a transfer to mechanical ventilation during the HBO course.

CONCLUSION

The inclusion of daily sessions (at least 4) of hyperbaric oxygenation in "soft" modes (1.4–1.6 ATA) in the complex therapy for COVID-19 has shown its safety and a preliminary positive effect on the subjective state of the examined patients and the dynamics of blood oxygen saturation.

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