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HYPERBARIC OXYGEN THERAPY IN COVID-19 TREATMENT: EFFICACY AND SAFETY

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ABSTRACT

Introduction: New effective treatments are sought to eliminate COVID-19-related hypoxia. Hyperbaric oxygen therapy is an effective method in the treatment of many diseases accompanied by hypoxia.
Aim: The aim of this study was to analyse the literature on the use of hyperbaric oxygen in the treatment of COVID-19 and to evaluate the effectiveness and safety of this method.
Materials and methods: Medical databases (Medline and PBL) and websites were reviewed using the terms hyperbaric oxygen and COVID-19. 25 works were qualified for the analysis.
Conclusions: The analysed literature shows that hyperbaric oxygen therapy is an effective and safe method of treating patients with COVID-19. Due to the limited amount of scientific evidence assessing the use of HBOT in COVID-19, there is a need for further research to confirm the effectiveness and safety of this method.
Keywords: hyperbaric oxygen, COVID-19, hypoxia.

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INTRODUCTION

The level of oxygen concentration in the atmosphere is on average 20.93-20.95 percent. (209- 460 ppm). The saturation of arterial blood with oxygen in a healthy person while resting at sea level should be 98%, i.e. it should contain 20.3 ml of oxygen in 100 ml of blood. HBO (hyperbaric oxygen) and NBO (ormobaric oxygen) are considered in qualification of patients to oxygen therapy. Changes in the lung parenchyma, which aggravate oxygen deficiency (hypoxia in the body) and lead to multi-organ failure, have been observed in patients with COVID-19 [1]. The main cause of mortality is respiratory failure. Numerous studies are being done to assess the efficacy and safety of treating COVID-19 patients based on the stage of the disease [2].

New methods of treatment are sought, using new achievements of oxygen therapy, in order to increase the effectiveness of treatment, minimize the risk of complications and reduce the mortality rate of patients with COVID-19. The choice of the appropriate method of oxygen therapy should be made very carefully, taking into account the accompanying diseases and the condition of the respiratory and circulatory systems [1]. Hypoxemic respiratory failure, which occurs in approximately 15–20% of hospitalized patients, requires supplementation with oxygen. Hyperbaric oxygen therapy (HBOT) has been proposed for the treatment of COVID-19-related hypoxia. HBOT is considered an effective therapy in all forms of oxygen deficiency. The method is non-invasive and used in basic or supportive treatment with different diseases. The effectiveness of the therapy has been documented in the case of arterial gas embolism, carbon monoxide poisoning, decompression sickness, crush injuries and diabetic foot ulceration [2].

Hyperbaric oxygen therapy is the use of pure oxygen under increased pressure (generally 2-3 atmospheres), which increases the level of oxygen in the blood (hyperoxemia) and tissues (hyperoxia) [2,3,4]. Increased pressure and oxygen bioavailability affect the multitude of applications of this method, especially in the areas of hypoxia, and its antimicrobial, immunomodulating and angiogenic properties [4].

HBOT improves circulation and increases the delivery of high pressure oxygen, which improves the efficiency of tissue uptake and oxygenation in COVID-19 patients. Hyperoxygenation of arterial blood with plasma oxygen has a strong anti-inflammatory effect and may be virucidal against COVID-19. Clinical improvement has been observed with the use of HBOT in patients with hypoxemia (oxygen deficiency in the blood) with COVID-19. The number of ICU admissions as well as the number of patients with the need to converting to mechanical ventilation has gone down [2].

Oxygen hyperbaria is considered a safe method with a low risk of complications. There are no contraindications for the use of this therapy in patients with infectious diseases. Not treated pneumothorax and respiratory failure requiring mechanical ventilation are contradictions. The conducted studies indicate that hyperbaric oxygenation may be a very important method of treating patients with pneumonia associated with SARS-Cov-2 infection, especially in the early stages of the disease. HBOT may also be beneficial during intubation [2].

AIM

The aim of the meta-analysis of 2020-2022 literature is to discuss the usage of hyperbaric oxygen therapy in COVID-19 patients and the evaluation of effectiveness and safety of the therapy.

MATERIALS AND METHODS

Materials and methods: The literature on online databases: Medline and PBL was reviewed using MESH keywords (hyperbaric oxygen and COVID-19). Materials searched have been limited to people and English language. The articled found were verified based on their title and abstract. Irrelevant records were excluded. The full texts of the remaining papers were analyzed on the basis of their consistency with the topic and eligible articles were identified. In the databases mentioned above 47 papers were found (45 in Medline and 2 in PBL). In the process of selection, which was based on the titles and abstracts, 15 articles were excluded. 32 articles were entered into a full-text selection, 24 of which were eventually included in this review. Online resources were searched using a Google search engine with the following keywords: hyperbaric oxygen and COVID-19. One work from the Society of Underwater and Hyperbaric Medicine was selected. Ultimately 25 works were qualified for the analysis, including 5 clinical trials.

RESULTS

1. In the systematic review on the effects of hyperbaric oxygen therapy used in COVID-19 Oliaei et al. Included eight articles from three countries. The studies were divided into clinical trials and case reports. There were 221 patients in researched groups. Three clinical trials were included, with 109 people in the study groups (20,32,57) and 90 people in the control groups. Also included are five case reports involving 14 people. In most studies HBOT below 1.5-2 atmospheres absolute (ATA) have been used for 90 minutes and then for 60 minutes. Studies have shown that the use of HBOT was beneficial and safe for patients. Most of them recovered after the therapy. Blood oxygen saturation increased after several HBOT sessions. Treatment adverse events were very limited to non-HBOT-related mild epistaxis, earache, and claustrophobia. HBOT seems to be a safe and effective method of oxygenation in COVID-19 patients. However, knowledge and proofs about the results and mechanism of hyperbaric oxygen therapy in COVID-19 are not sufficient due to the small number of studies and the lack of large patient groups. Therefore further extensive research is needed [2].

Despite the evidence of improved breathing, HBOT has not yet been included in guidelines for severe COVID-19 patients. More randomized clinical trials in a larger number of patients are needed to obtain convincing evidence that hyperbaric oxygen therapy is an effective treatment option for patients with COVID-19 and its inclusion in the guidelines for therapeutic management of patients with COVID-19 [2].

The discussed studies show that HBOT is beneficial for patients by increasing the oxygen pressure in the alveoli. The rate and degree of oxygen diffusion is better in comparison to to standard oxygen therapy (face mask, nasal cannula, invasive ventilation, non-invasive

ventilation and ECMO (extracorporeal blood oxygenation)). HBOT provides better tissue perfusion due to increased oxygen diffusion, which differs from other methods of oxygen therapy. Patients undergoing HBOT show improvement in: arterial blood gasometry, liver function tests, blood count and lung condition [2].

Patients with COVID-19 require special monitoring in hyperbaric chambers (electrocardiography, pulse oximetry, temperature measurement) [2].

The results of studies on the use of HBOT in patients with COVID-19 are promising. This method of delivering oxygen reduced the severe symptoms of COVID-19 and improved the general well-being of the treated patients, as well as corrected hypoxia and increased oxygen saturation.

Research analysed by Oliaei et al. show that HBOT reduced mortality. Only in one study the mortality rate was of 10% (2 out of 20). In the remaining analysed studies (7 studies, 101 participants) no fatal case was reported, but this may be due to the limited size of the studied population [2].

The review of research shows that HBOT is one of the most effective and safest methods of compensating for oxygen deficiency in acute respiratory distress syndrome. In HBOT chambers, patients breathe naturally and therefore do not experience any serious side effects. With the use of pressures usually exceeding 2.0 ATA, other diseases than COVID-19 sometimes resulted in injuries to the middle ear, lung barotrauma, oxygen toxicity mainly related to the central nervous system and eye disorders. One of the main disadvantages of HBOT is the limited availability of the method or their lack. The need for a large space to perform HBOT and the limited availability in many facilities may make it difficult to use this method during the pandemic. In many centres there are deficiencies even in the case of standard oxygen supply, and hyperbaric treatment requiring appropriate conditions may not be available there. As a result, only a limited number of patients have access to this treatment method [2]**.**

It was concluded by Oliaei et al that knowledge and proofs on HBOT positive effect on COVID-19 are limited. Therefore, to evaluate this treatment results precisely and to compare it with other oxygen-associated methods, there is a need for further research with a larger number of people [2].

2. Criado et al. in their review discussed some research on HBOT in COVID-19 patients. They took into account the study by Zhong et al., who described the first case of successful hyperbaric oxygen therapy in a seriously ill patient with COVID-19 in February 2020. For this patient standard respiratory support had failed. The improvement occurred after eight HBOT sessions at 200 kPa. The total treatment time was 95 minutes [3]. Criado et al. also discussed the research by Chen et al., who described five cases of severe or moderate course with acute respiratory distress syndrome (ARDS). Pneumonia was treated with the HBOT method. These five patients (24-69 years) received three to eight sessions of HBOT in addition to routine therapies. One patient was compressed with 2.0 ATA and the other four with 1.6 ATA for 15 minutes. The bottom time in the first treatment was 90 minutes, and in the second - 60 minutes.

Decompression to atmospheric pressure took place within 20 minutes. The average daily oxygen saturation (SpO_2) was restored to over 95% after one to eight HBOT treatments. Blood oxygen partial pressure (PaO_2) and blood hemoglobin oxygen saturation (SaO_2) levels also increased significantly, and lactate levels decreased. The number of lymphocytes was markedly increased, and the serum levels of fibrinogen and D-dimer decreased. Chest CT scan during or after HBOT showed regression of inflammatory lung lesions in each patient [3]. The risk of transmission of infection in a hyperbaric chamber is not greater than in the ward. For COVID-19 patients, disease control measures outside the chamber were the same as in infectious diseases wards. The disinfectants in the chamber have been strengthened to the level of infectious wards [3].

Criado et al. also took into account the similar results of the HBOT treatment of patients with COVID-19 obtained by Guo et al. The patients were subjected to a pressure of 1.5 ATM with an oxygen concentration above 95%. The procedure was done for one week once a day for 60 minutes. The patients' condition gradually improved. The oxygen saturation level significantly improved and the number of lymphocytes increased. Chest CT scan showed a clear subsidence of inflammatory changes in the lungs [3]. Major side effects of HBOT concern lungs (irritation of the trachea and bronchi) and neurological symptoms (e.g., visual disturbances, tinnitus, facial spasms, dizziness, confusion, and nausea). Due to the limited number of COVID-19 patients for whom HBOT may be considered, it is difficult to assess the extent of side effects of this therapy [3].

3. The need for intubation and mechanical ventilation in COVID-19 patients is associated with high mortality and a significant burden on the health care system. In contrast, treatment with hyperbaric oxygen is a non-invasive method with a low risk of complications and may be beneficial for patients with COVID-19. The systematic review carried out by Boet et al. was designed to test the effectiveness and safety of HBOT in the treatment of COVID-19. Six publications (one cohort study and five case reports) were selected for a total of 37 patients with COVID-19 hypoxaemia treated with HBOT. The need for intubation and mechanical ventilation as well as in-hospital survival were assessed in 26 patients. Intubation and mechanical ventilation were not required in 24 patients and 23 survived. No serious side effects have been reported. The analysed studies suggest that HBOT is safe and may be an effective method of treating patients with hypoxaemia during COVID-19. Randomized controlled trials are needed to confirm the conclusions [5].

4. In a review of studies on the use of HBOT in COVID-19, De Maio et al. showed that hyperbaric oxygen therapy may be a useful method of improving the health of COVID-19 patients, especially when the intervention occurs early in the disease, although it can also be successfully used during the intubation period. There is, however, a logistics problem in using HBOT at ICU, because hyperbaric chambers take a lot of space and cannot be available in the ward, and patients have to be transported to HBOT facility. Portable chambers that could be easily installed near the patient's bedside in the ICU would be useful. Despite the very enthusiastic attitude to the positive role of HBOT in the treatment of

COVID-19, clinical trials are needed to see if this therapy can save lives [6].

The initial stage of pneumonia in COVID-19 is understood to be "silent hypoxia", in reference to its "insidious, hard-to-detect nature". With oxygen saturation levels falling from the normal range of 94-100% to as low as 50%, patients may not experience shortness of breath until levels have dropped to critical levels as CO2 continues to be released. By the time CO2 builds up, causing them to feel breathless, many patients with COVID-19 develop respiratory failure rapidly [6].

The use of HBOT in early intervention before mechanical ventilation is needed can be very useful in saving lives and improving health. The great advantage of HBOT is the supply of oxygen at elevated partial pressure, which causes the gas to penetrate the tissues very quickly and in a higher concentration. This is more efficient than delivering oxygen to the hemoglobin [6].

5. In their research Kjellberg et al. discussed a positive impact on using hyperbaric oxygen therapy in case of COVID-19, which was shown in two serious cases in Wuhan, China. In both cases, health improved by increasing blood oxygen saturation and reducing inflammation in the lungs. The authors also discussed the case of five Louisiana patients treated with hyperbaric oxygen, whose symptoms after HBOT were immediately relieved and all were gone after 1-6 treatments, without intubation and mechanical ventilation. In addition, HBOT has been reported to be safe when using mechanical ventilation [7].

The authors believe that experimental and empirical data suggest that hyperbaric oxygenation may reduce the inflammatory response to COVID-19. However, there are concerns about the safety of this method in patients with viral pneumonia [7].

6. Dr Harch, in his comment to two Chinese research, created a graph of the oxygen saturation of five patients. Measurements of oxygen saturation show that intermittent high doses of oxygen are the key to the effective treatment of COVID-19 infections (fig. 1) [8].

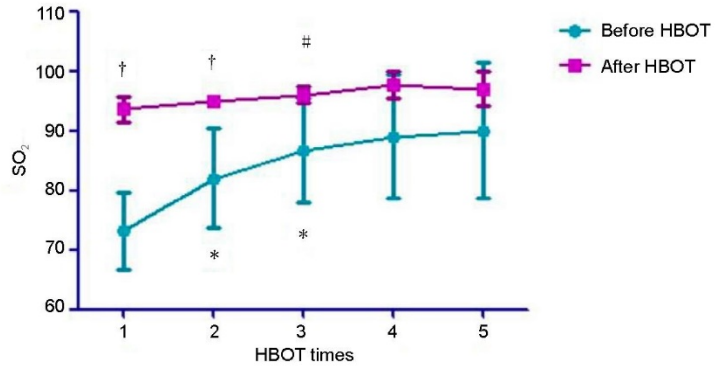

Fig. 1. Average daily blood oxygen saturation levels before and after each HBOT use in five COVID-19 patients [8].

According to James data in the picture 1 in Harch article shows that:

- Patients with COVID-19 have an increased diffusion resistance to oxygen - hence very low oxygen saturation. Oxygen saturation increases with each session.
- This resistance can be overcome by using high oxygen concentrations in a simple pressurized housing.
- There has been an increase of the improvement with each session.
- The improvement shows that oxygen heals the underlying pathology and eliminates oedema.
- Oxygen is therefore used as a treatment rather than simple blood supplementation [9].

7. In their paper Ylikovski et al. refer to Harch's article summarizing the clinical results of six COVID-19 patients. Four had a milder form of respiratory failure, one had pneumonia, and one had acute respiratory distress syndrome (ARDS). All patients were treated with oxygen for several days, but their oxygen saturation levels did not improve. After using HBOT, oxygenation immediately began to improve, and after 3–8 treatments the patients were discharged from the hospital. The authors also suggested that the use of HBOT in the early stages of the disease process could prevent severe COVID-

19 infection. Ylikovski et al. fully agree with this suggestion. They also believe that the use of HBOT in a COVID-19 patient with confirmed hypoxia who does not respond rapidly to oxygen ventilation therapy could prevent the progression of lung disease.

According to Ylikovski et al. HBOT is a safe, effective and non-invasive method of treatment, which can correct tissues hypoxia. Under hyperbaric conditions, the voltage of oxygen plasma increases from 95 mmHg to over 2000 mmHg, which increases the gradient or the penetration of oxygen into the tissues by 20-times. During HBOT, more oxygen is dissolved in the blood plasma. HBOT is much safer than any of the drugs currently being tested because the serious side effects of this method do not occur in practice. Many studies report that HBOT increases parasympathetic (vagal) activity and has a strong anti-inflammatory effect. Using HBOT can be beneficial at all stages of COVID-19 [10].

8. The Geier work discusses the principles of oxygenating the body with the use of hyperbaric oxygen therapy. HBOT aims to increase the level of oxygen in the blood. The patient is placed in a sitting or lying position in a closed chamber. The pressure in the chamber increases and 100% oxygen is delivered. The pressure is expressed in multiples of the atmospheric pressure at sea level, i.e. 1 atmosphere. The concentration of oxygen in the blood (plasma) at sea level is 0.3 ml per decilitre. Resting tissues extract 5 to 6 ml of oxygen per decilitre of blood when properly perfused. The administration of 100% oxygen at a pressure of 1 atmosphere increases the amount of oxygen dissolved in the blood by 5 times, to 1.5 ml per decilitre. At a pressure of 3 atmospheres, the dissolved oxygen content is approximately 6 ml per decilitre. Such level is higher than sufficient to oxygenation the cells without the participation of oxygen associated with haemoglobin. Therefore HBOT can provide adequate oxygenation in the cases of respiratory disorders related to COVID-19 [11].

9. The studies analysed by Ortega et al. show that HBOT can be used in patients with the severe form of COVID-19 disease, as well as during recovery from SARS-CoV-2 infection. Clinical trials have demonstrated the potential use of HBOT to redirect hypoxaemia-delayed O2 diffusion and to eliminate inflammatory cytokines.

HBOT can also be used in the treatment of the so-called "Silent" hypoxaemia in patients who are not yet in a severe clinical course. Quiet hypoxaemia in critically ill patients is not characterized by typical respiratory failure, but if undetected, it may be dangerous as it may deteriorate very rapidly. Studies have shown an association between hypoxaemia and mortality in COVID-19 patients [4].

In the analysed studies, it was observed that patients with COVID-19 also develop hypoxaemia without dyspnoea. Some people with mild or no symptoms, who developed multi-organ failure and a fatal outcome, usually had low pulmonary heart rate readings. In patients who have no history of respiratory problems, it is advisable to use pulse oximetry to predict the hypoxaemia/hypocapnia syndrome that defines asymptomatic hypoxia. [4].

The studies showed a higher rate of oxygenation in the supine position in relation to variables such as gravity, lung structure and higher expression of nitric oxide (NO) in the dorsal pulmonary vessels compared to the abdominal ones.

In vitro studies have shown that HBOT increases the production of NO and ROS / RNS (reactive oxygen species / reactive nitrogen species), inhibiting the replication of SARS-CoV-2 [4].

A study on the use of HBOT in a patient with a severe course of COVID-19, compared to normobaric oxygen supply, showed a better result with the use of hyperbaric oxygen therapy. Positive results of COVID-19 treatment connected with finding a weakening of the innate immune system and an increase in tolerance to hypoxia have been shown. HBOT therapy was assessed as supporting the mitigation of the cytokine storm (rapid cytokine surge by the immune system). The safety and efficacy of HBOT in COVID-19 patients has been well assessed compared to mechanical ventilation. Another study showed rapid relief of hypoxaemia with HBOT treatment from baseline in patients with COVID-19 pneumonia [4].

The analysed studies show that the use of HBOT in patients with COVID-19 may contribute to the reversal of hypoxaemia and the improvement of circulatory diffusion in the pulmonary capillaries. HBOT leads to an increase in the O2 pressure in the alveoli above the ambient pressure, which results in a large, more than 10-fold, increase in O2 diffusion into the lung capillary circulation, in order to reach the plasma and tissues independently of Hb. There is an increase in the supply of O2 to the tissues through the increase in pressure. Experimentally, the hematological, biochemical and inflammatory parameters improved significantly after the use of HBOT. The studies showed an increase in the number of lymphocytes and a decrease in the level of lactate and fibrinogen [4].

Patients may suffer from desaturation reflexes during HBOT. The aetiology of this reflex is unclear, it is probably caused by spasm of the pulmonary arteries as a result of oxidative stress, direct damage to type II pneumocytes, or a COVID-19-related thrombus [4].

Ortega et al. emphasise that despite ongoing clinical tests, HBOT is not yet an indication for use with COVID-19, but may be recommended for the consequences of viral infections. More research is still needed to confirm its beneficial effects. They would also justify the creation of hyperbaric chambers in hospitals [4].

10. The work analysed by Feldmeier et al. shows that treatment with hyperbaric oxygen offers several potentially beneficial therapeutic effects. The conducted studies demonstrated the effectiveness and safety of using hyperbaric oxygen. HBOT provides oxygen under conditions of extreme hypoxaemia and tissue hypoxia, even in the presence of lung lesions. In COVID-19 patients, it exhibits anti-inflammatory effects and is likely to moderate the over-immune response. Unlike steroids, it does not cause immunosuppression. One study suggests that HBOT may reduce hypercoagulability in patients with COVID-19. The use of hyperbaric oxygen probably solves the oxygen debt problem that can arise from prolonged hypoxaemia and tissue hypoxia [12].

11. Kipshidze et al. stated that the research analysed by them suggest that HBOT can restore proper oxygenation in patients with COVID-19 successfully. Early use of HBOT can improve general systemic supportive care, reduce the use of mechanical ventilation, and

significantly improve the outcomes of COVID-19 patients. Preliminary evidence strongly suggests HBOT is useful in severe hypoxaemia in patients with COVID-19 pneumonia [13].

12. El Hawa et al. emphasise that although COVID-19 is not currently an indication for HBOT, patients may be referred for HBOT due to the post-infectious sequelae of viral infection. HBOT facilities need to know the potential applications of this treatment in the case of post-viral complications [14].

In El Hava et al. paper the role of HBOT centre in COVID-19 chronic effects has been described. Patients with acute COVID-19 infection have not been treated. Referrals included patients with dyspnoea, acute limb ischaemia, sudden sensorineural hearing loss, acute anemia, dysgeusia, persistent fatigue and malaise following COVID-19 infection [14].

13. Literature analysis by Perdrizet et al. shows that HBOT can be used in the treatment of COVID-19 because it can directly reverse tissue hypoxia and have anti-inflammatory properties. The authors included in their work several reports confirming the use of HBOT for the benefit of patients infected with SARS-CoV-2 with symptoms of lung damage and dysfunction [15].

14. The literature analysed by Moon et al. shows that resistant hypoxaemia associated with COVID-19 can be treated with hyperbaric oxygen due to the increase in the partial pressure of inhaled oxygen. However, the time of safe administration of HBO in the chamber is limited due to problems with confinement and isolation from other necessary medical interventions and due to the toxicity of oxygen [16].

15. A review of the literature conducted by Paganini et al. shows that in the face of the COVID-19 pandemic and the related overload of health care, increased need for hospitalization and equipment, the use of intermittent hyperbaric oxygen therapy in sick patients resulted in overcoming progressive hypoxaemia during maximum ventilator support. In less severe cases with the risk of hypoxaemia, the applied hyperbaric oxygen therapy prevented intubation and led to a rapid relief of symptoms [17].

16. Simon in his article emphasise that, with no doubt, hypoxia may improve during the use of HBOT in a critically ill patient with Covid-19. It is not known if HBOT is antiviral. However, there are potentially beneficial immunomodulatory and anti-inflammatory effects of HBOT therapy. The use of this method is associated with some logistic difficulties, such as the transfer of patients from Covid-19 to hyperbaric chambers, staff protection, infection control and the challenges of caring for very sick patients during HBOT. Any hyperbaric dose of oxygen may favor pulmonary oxygen toxicity. There is a possibility that COVID-19 may increase the risk of developing pulmonary barotrauma. According to Simon, the balance between the potential benefits and risks of using HBOT in the treatment of COVID-19 is not based on sufficient scientific evidence [18].

17. UHMS (Undersea & Hyperbaric Medical Society) strongly advocates for well-designed clinical trials of the use of hyperbaric oxygen in the treatment of COVID-19. UHMS sees the particular value of randomized controlled phase III trials in providing evidence and strongly supports the funding and conduct of these trials. UHMS also recognizes that an off-protocol COVID-19 treatment at the physician's discretion may be appropriate in some cases. UHMS strongly encourages good documentation of the scientific observations of the impact of HBO2 in the treatment of COVID-19 patients, treatment methodology and patient selection criteria [19].

18. UHMS in the paper titled.: *„Rationale, Study design considerations and protocol recommendations for treating COVID-19 patients with hyperbaric oxygen"* proves that hyperbaric oxygen therapy has a positive effect on COVID-19 patients. In addition to the very high oxygenation of the body, the positive effect of HBOT on the immune system was indicated [20].

Some COVID-19 patients develop an excessive immune response, which generates inflammatory and pro-inflammatory reactions, leading to damage to the lungs, kidneys, gastrointestinal tract and other systems and organs. A phenomenon known as "cytokine storm" is often observed in patients. Many of them need to be connected to a respirator and then die. In other disease entities (blood vessel necrosis, traumatic brain injury) it has been proven that HBOT reduces the elevated level of cytokines to the normal range. HBOT also has a positive effect on patients with pancreatitis, ulcerative colitis or sepsis. HBOT can improve outcomes in acute inflammation. This is very important for COVID-19 patients. The clinical studies conducted so far in patients with COVID receiving HBO2 do not indicate that hyperbaric oxygen interrupts or reduces hypercoagulability in the advanced stage of SARS-CoV-2 infection. The use of HBOT in patients with COVID-19 may bring benefits in reducing the oxygen debt arising from long periods of hypoxaemia [20].

The work of UHMS shows that the use of hyperbaric oxygen in patients with COVID-19 affects the reduction of hypoxia, deep inflammatory response, hypercoagulability and oxygen debt.

In patients with COVID-19 treated with HBOT, there is sustained improvement of hypoxia after the end of therapy, repayment of the accumulated oxygen debt, reduction of inflammation and improvement of hypercoagulation [20].

RESULTS OF CLINICAL RESEARCH REVIEW

1. Gorenstein et al. evaluated safety and effectiveness of hyperbaric therapy in patients with breathing problems in COVID-19. They considered high mortality rate and prolonged duration of mechanical ventilation of patients. Conducted a single-centre clinical trial, from 1 to 14 days of hospitalization, 20 patients with COVID-19, aged 30-79 years, with a BMI from 19 to 42, who received hyperbaric oxygen therapy in single-site hyperbaric chambers at a pressure of 2.0 atmospheres for 90 minutes, five times a day maximum. The oxygen demand was from 2 to 15 litres. Out of the examined patients, two (10%) required intubation and died, 18 (90%) in good condition were discharged from the hospital. Several adverse events occurred during hyperbaric oxygen therapy, such as: epistaxis (not directly related to HBOT), ear pain and claustrophobia. By increasing the concentration of oxygen in the body, hyperbaric oxygen therapy improves health. HBOT is

a safe and effective method of treating patients with COVID-19 [21].

2. Guo et al. studied two men aged 57 and 64 to determine the effectiveness of hyperbaric oxygen therapy in improving hypoxaemia in patients with severe COVID-19 pneumonia. Each of them met at least one of the following criteria: dyspnoea; respiratory rate (RR) of 30 breaths / minute; oxygen saturation (SpO2) 93% at rest; oxygen index (ratio P / F: PaO2 / FiO2 300 mmHg). In each case, pneumothorax and other absolute contraindications to HBO2 were excluded. The patients were treated for a week, once a day for 60 minutes at a pressure of 1.5 ATM and an oxygen concentration above 95%. In both patients, shortness of breath and shortness of breath were alleviated after the first treatment, and a definite improvement was felt after seven days of therapy. RR was also falling day by day. Neither of the patients were in critical condition. SO2 and P/ F increased day by day. Lymphocyte counts and ratios also gradually returned to normal. The level of D-dimers has dropped. A chest CT scan showed that the pneumonia had clearly resolved [22].

Initial case reports suggest that HBO2 therapy may rapidly improve hypoxaemia in patients with COVID-19 pneumonia. However, the limited sample size precludes confirmation of the potential efficacy of HBO2 therapy for COVID-19 pneumonia. Randomized clinical trials are required for further evaluation [22].

3. In their work Thiobodeaux et al. described the HBOT treatment of five COVID-19 positive patients (four women and one man). All patients had rapid breathing and low oxygen saturation despite receiving high FiO2 (oxygen fraction in inhaled air). HBOT was used to prevent mechanical ventilation. Oxygen was applied at a pressure of 2.0 ATA for 90 minutes. Patients received from one to six treatments. All patients recovered without the need for mechanical ventilation. The improvement in health occurred in less than 24 hours. With the use of HBOT, oxygen saturation increased, rapid breathing subsided and inflammatory markers decreased. At the time of writing, three of the five patients had been discharged from the hospital, and the remaining two were stable. A very large improvement in health has been shown thanks to the use of HBOT. This method prevented the need for mechanical ventilation. There were no complications associated with HBOT treatment. The results are similar to the case series from Wuhan, China [23].

After the spread of COVID-19 in the United States, doctors began considering HBOT as part of a treatment regimen for COVID-19 patients. There are no contraindications for the use of HBOT in viral pneumonia or SARS. The only absolute contraindication to the use of HBOT is untreated pneumothorax [23].

4. The so-called long COVID is a common occurrence following COVID-19 infection. The most common symptom is fatigue. Intervention treatment options are limited. For long COVID, one treatment option is hyperbaric oxygen therapy. Robbins et al. studied 10 patients with long COVID who received 10 HBOT sessions to 2.4 atmospheres within 12 days. Each treatment lasted 105 minutes and consisted of three 30-minute injections of 100% oxygen, interspersed with 5-minute breaks. Fatigue assessments and a cognitive scale were performed on days 1 and 10. The use of HBOT resulted in a statistically significant improvement in the Chalder fatigue scale (very large), global cognition (large), executive functions (large), attention (very large)), information processing (very large)) and verbal function (large). The presented results suggest the potential benefits of using HBOT, however, the results are statistically significant after 10 sessions [24].

5. Cannellotto et al. analysed the safety and efficacy of HBOT in the treatment of hypoxaemia in patients with COVID-19 and assessed the time needed to correct hypoxaemia [25].

To this end, they conducted a multicentre open-label randomized controlled trial involving 40 patients (20 in each group) with COVID-19 and severe hypoxaemia who were unable to achieve 90% oxygen saturation despite supplementation. Patients were assigned to 7 days of HBOT treatment or standard treatment of respiratory symptoms. Hyperbaric oxygen therapy was planned for 5 sessions (1 / day) for 90 minutes at a pressure of 1.45 ATA. The results included the time needed to normalize the oxygen demand to 93%, the need for mechanical respiratory assistance, the occurrence of acute respiratory distress syndrome and the 30-day mortality. Dyspnoea was a frequent symptom of patients on admission. SpO2 for the entire group was 85.1% ± 4.3%. The treated group received an average of 6.2 ± 1.2 sessions of HBO2. The time needed to correct hypoxaemia was shorter in the treatment group (median 3 days) compared to the control group (median 9 days) [25].

The performed treatment had no statistically significant effect on the occurrence of the acute respiratory distress syndrome, mechanical ventilation and death within 30 days of admission. The study confirmed the safety and efficacy of HBOT in the treatment of patients with COVID-19 and severe hypoxaemia. Larger clinical trials are needed to further confirm the survival impact of HBOT treatment [25].

CONCLUSIONS

1. The literature review on HBOT usage in COVID-19 shows that hyperbaric oxygen therapy is a safe and effective method of COVID-19 patients' treatment.
2. The conducted clinical trials indicate that hyperbaric oxygenation may be a very important method of treating patients with pneumonia associated with SARS-Cov-2 infection.
3. HBOT improves the oxygenation of patients with COVID-19 pneumonia and increases the chance of survival.
4. Hyperbaric oxygen therapy is associated with a very low risk of complications. There are no contraindications for its use in patients with COVID-19.
5. A limited number of studies indicate the need for further clinical trials to confirm the efficacy and safety of HBOT in the treatment of patients with COVID-19.

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