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Hyperbaric oxygen therapy as a supportive therapy for COVID-19 patients: a narrative review

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Abstract. **The Coronavirus illness 2019 (COVID-19) was first observed to induce fever, dry cough, pneumonia, and dyspnea in the lower respiratory tract. Atypical manifestations, including digestive problems and cardiac symptoms, were also observed. The rate of mortality in the older population is greater than in the younger group, as well as in individuals suffering from comorbidities. Oxygen supplementation through a facemask, non-invasive ventilation, mechanical ventilation, and extracorporeal membrane oxygenation ECMO are some of the available supportive techniques. Hyperbaric oxygen treatment (HBOT) is thought to boost tissue oxygenation by increasing plasma soluble oxygen levels. HBOT also reduces inflammatory responses in COVID-19 patients, minimizing the negative impacts of the cytokine storm. Because the existing data on the efficacy of HBOT in COVID-19 patients is limited, the purpose of this article is to review the possible mechanisms of HBO, as well as data available on potential advantages, side effects and uses in the treatment of COVID-19 patients.**

Key Words:
Hyperbaric oxygenation therapy, COVID-19, Respiratory distress syndrome, Pneumonia.

Abbreviations

ECMO: Extra Corporeal Membrane Oxygenation; HBOT: Hyperbaric Oxygen Therapy; SARS: Severe Acute Respiratory Syndrome; CO2: Carbon Dioxide; ICU: Intensive care Unit; CBC: Complete blood count; CT: Computed tomography; HIF: Hypoxia-Inducible Factor; SpO_2: Saturation of Peripheral Oxygen.

Introduction

Coronavirus disease (COVID-19) is a serious respiratory infection produced by the severe acute respiratory syndrome SARS-CoV-2 virus, which had first emerged as a new human disease in China in late 2019 and remains a global pandemic[1-4]. The greatest common symptoms are pneumonia, dry cough, high fever, chest pain andmyalgia[5-9]. COVID-19 has a mortality rate ranging from 1% to over 7%, with respiratory failure being the most common cause[10,11].

According to the most recent findings in pathological anatomy, COVID-19 principal pathological abnormalities were alveolar inflammation and mucilaginous secretion. The most common symptom of progressive COVID-19 pneumonia was increasing hypoxemia[12-15].

To avoid contracting COVID-19, the Japanese government advised people to wear a mask, stay 2 meters away from others, frequently disinfect hands with alcohol, keep away from unnecessarily going out and avoid the three Cs of "closed spaces with poor ventilation, crowded spaces with many people and the close contact"[16].

The risk of SARS and death was higher in the elderly and in patients with many comorbidities. Furthermore, an increased D-dimer on admission as a result of fibrinogen degradation that signaled a prothrombotic condition was linked to a bad prognosis[17,18]. Finally, once the patient required artificial ventilation, the patient's chance of death rose[12].

COVID-19 associated hypoxia has been treated with hyperbaric oxygen treatment (HBOT)[19,20]. HBOT has been shown to be successful in treating any type of oxygen deficiency[21]. HBOT is a non-invasive treatment that can be used to treat a variety of medical diseases as a primary or supplementary therapy[22]. HBOT is now used to treat disorders, including gas embolism, CO_2 and cyanide poisoning, severe anemia, and other pathologic conditions[23].

HBOT is used to treat both elective and emergency medical issues, such as soft tissue radiation effects and non-healing chronic wounds, e.g., carbon monoxide toxicity, decompression

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illness and gas embolism[24]. In addition, late effects of radiation therapy, necrotizing fasciitis and compromised flaps are among the indications for HBOT[25].

HBOT is a technique for increasing the quantity of dissolved oxygen in the tissues by using high concentrations of oxygen 100% at an atmosphere pressure greater than one absolute atmosphere inside a chamber[26,27].

This review is an attempt to collect some information about the studies that used HBOT as an adjunctive treatment for helping people with COVID-19.

HBOT and Its Mechanism for Improvement of Symptoms of COVID-19

In HBOT, patients breathe 100% pure oxygen at high pressure. This might assist cell oxygenation throughout every level, from pulmonary function to alveolar oxygen exchange to hemoglobin capacities[28].

HBOT can alleviate hypoxia in COVID-19 patients by increasing circulation and oxygen delivery under high pressure, improving tissue uptake and reducing hypoxia[29]. Furthermore, HBOT has a potent anti-inflammatory impact and may have a directly truthful action on COVID-19 by hyper-oxygenating arterial blood with plasma-dissolved oxygen[20]. HBOT treatment in hypoxemic COVID-19 patients has been shown to enhance clinical outcomes, such as reducing ICU admission and preventing the need for mechanical ventilation[21,30,31].

HBOT is thought to be a low-risk and safe procedure[32]. In patients with viral, bacterial, or fungal infections, there are no contraindications to the administration of HBOT[33]. Untreated pneumothorax and respiratory failure patients who require mechanical ventilation are the only main contraindications to HBOT[30]. According to recent studies[29], HBOT may be a critical treatment for improving outcomes in patients with COVID-19 pneumonia, especially in the early stages and it may also be beneficial throughout the intubation phase.

Patients benefit from HBOT because it increases the oxygen pressure in the alveoli as a result. When HBOT matched to traditional oxygen therapy (e.g., face mask, non-invasive ventilation, invasive ventilation, nasal cannula and extracorporeal membrane oxygenation), the oxygen diffusion rate will rise. HBOT distinguishes itself from all other oxygen therapy techniques by providing tissue perfusion exchange capability due to higher oxygen diffusion rate. In patients who had HBOT, the following clinical parameters and indicators improved: blood gas analysis, liver function, full blood count CBC and enhanced lung structural clearances established on computed tomography CT-scan[34].

Several meaningful findings[35-37] point out that HBOT has a favorable effect on the prevalent long-term COVID-19 symptoms of exhaustion and 'brain fog'. These findings corroborate the clinical and qualitative observations of patients who have received the treatment and reported that their lives have been changed. Long COVID-19's mechanism is currently unknown. Long COVID-19 may be characterized by a wide range of alterations, as a result of prolonged tissue hypoxia, according to one theory[38]. This is frequently the common denominator in many HBOT-responsive illnesses.

The advantages of HBO therapy over ambient oxygen absorption are as follows: an enhanced oxygen diffusion distance; higher physically dissolved oxygen content in the blood, which is more than the total hemoglobin transport capacity and improved oxygen diffusion effectiveness through the alveolar barrier. These characteristics, taken combined, meet the need for aerobic metabolism in hypo perfused areas of the body[39].

Overall, HBO's actions could counterbalance several changes lately seen in COVID-19 patients, such as aggregation, coagulation problems and immune system dysfunction. Daily HBO therapies, for example, may minimize platelet motivation plus aggregation in the lungs, preventing the progress of respiratory microcirculation malfunction and disastrous inflammation, which have previously been described in pathologic research[40-45].

Patients in HBOT chambers breathe naturally, therefore substantial respiratory interventions like mechanical ventilation are unlikely to cause serious side effects. Previous studies employing HBOT for different health concerns documented complications include middle ear and pulmonary barotrauma, oxygen poisoning mostly impact the central nervous system and ocular symptoms with administered pressures typically exceeding 2.0 ATA[46]. Mild epistaxis not linked to HBOT, earache and claustrophobia were reported as treatment side effects[47].

HBOT may have a big drawback in terms of accessibility, as there are already limitations in normal oxygen distribution and HBOT is likely to be less accessible in numerous centers[48].

Application of HBOT: Time and Pressure

Patients inhale 100 % oxygen at 1-1.5 time's atmospheric pressure in the hyperbaric chamber. As the pressure rises, the amount of dissolved oxygen in the plasma and tissues rises as well. HBOT has the potential to cure severe COVID-19 disease symptoms, such as hypoxic and respiratory problems. The specific reason for the phenomenon is unknown. Hyper oxygen saturation, on the other hand, could have a variety of antiviral actions, such as increasing the amounts of viricidal oxygen free radicals[49], upregulating hypoxia-inducible factor HIF that promotes the production of antiviral peptides like defenses and lowering pro-inflammatory cytokines like IL-6, which are responsible for cytokine storm[12,50].

Over the course of 12 days, patients with extended COVID-19 got 10 HBOT sessions, one every day at 2.4 atmospheres for 1 hour and 45 minutes with a 2-day break in the middle for the weekend. Using established scales, the researchers found statistically and clinically significant improvements in the overall fatigue score as well as a variety of cognitive domains[35].

Every patient with a medical hyperbaric chamber received HBOT once a day. The exclusive passage allows patients to access the hyperbaric chamber. Patients inhaled oxygen using the built-in breathing apparatus (BIBS) as soon as they entered the chamber and continued to do so until the conclusion of decompression, with no breaks for infection control measures. In 15 minutes, the room was crushed to 2.0 ATA absolute pressure for patient No. 1 and 1.6 ATA for the remaining patients with air. The first treatment took 90 minutes, and the second took 60 minutes. It took 20 minutes to decompress to atmospheric pressure[28].

The majority of research has used oxygen at 1.5 to 3.0 atmosphereabsolute ATA, a range in which the danger of side effects is minimal while therapeutic outcomes are obtained. Additionally, HBOT is a critical technique for enhancing cardio-respiratory function in individuals with ARDS, according to other studies[39]. COVID-19 has been linked to an increase in plasma CRP concentrations[51-53].

Studies about HBOT and COVID-19

Case series[17,31] of patients with COVID-19 disease revealed that, following a single HBOT treatment, patients stated that their difficulty of breathing had resolved quickly. The improvement in symptoms was associated with an increase in oxygen saturation readings, as expected. It took between one and six HBOT sessions to reduce oxygen requirements below 50% FiO_2, with an average of five HBOT treatments per patient attaining the primary goal of eliminating mechanical ventilation.

Other studies[39,47,51] were conducted on patients with COVID-19 related hypoxia using HBO_2 to alleviate their hypoxia. HBO_2 may excite stem cells, prevent the inflammatory pathway, conflict with the establishment of interstitial fibrosis in the lungs, slow the advancement of serious interstitial pneumonia, and reduce the risk of cross failures due to a lower COVID-19 viral load.

HBOT supplied the body with an adequate aerobic metabolism intermission. Most patients with severe COVID-19 may only require two HBOT treatments to remediate hypoxia. In COVID-19 pneumonia patients having an oxygen saturation of less than 70%, the regular daily HBOT regimen might actually prevent hypoxia. HBOT's benefits for enhancing oxygen delivery and tissue perfusion, immunologic function and lung illness are all supported by this research. HBOT is a significant intervention for COVID-19 pneumonia patients who are severely unwell or dangerously ill. When mask oxygen breathing failed to keep the patient's SpO_2 from dropping, they advised that early supplemental HBOT could prevent the patient's condition from deteriorating. The addition of daily HBOT to conventional supportive therapy would minimize mortality[28].

HBOT could be a promising treatment option for COVID-19 patients. It is safe when mechanical ventilation is used. A tiny Chinese trial[52] found that it has a lot of potential for treating COVID-19 patients. Five critically sick patients with COVID-19 suffering from hypoxia-like symptoms were given HBOT in this study. According to CT scans, the patients' clinical condition improved dramatically after two treatments, with an increase in blood oxygen saturation and decreased lung inflammation. There were no fears about virus contamination nor disease spread among medical personnel.

The two most common illnesses among the patients who needed mechanical breathing during HBOT were carbon monoxide poisoning and iatrogenic gas embolism. Throughout hyperbaric oxygen therapy, mechanical ventilation is a safe option for patients. To prevent patient-ventilator asynchrony, sedation must be perfected[53].

In a prospective, multi-center, open-label randomized controlled trial[54] of hyperbaric oxygen HBO_2 as an adjunctive therapy for COVID-19 in-

dividuals with symptomatic hypoxemia, the trial involved 40 patients that were unable to reach an oxygen saturation of 90% despite oxygen supplementation, 20 in the HBO_2 treated group and 20 in the controls no HBO_2 arm. The study did not discover any improvements in acute respiratory distress syndrome, mechanical ventilation, or death, but this is likely due to the study's small sample size and the selection of a potentially less essential patient cohort. However, the authors demonstrated a definite gain in terms of fewer days due to an increase in oxygen needs.

The HBOT use on patients with COVID-19 and severe respiratory symptoms was published by Harch[34], who carried out the research at the Wuhan Yangtze River shipping general hospital. The HBOT use showed fast relief of symptoms related to hypoxia, improvement of hypoxemia, appetite improvement, reduction of headache and sense of well-being, clinical objective indicators such as differential count, coagulation profile, arterial blood gas values, liver function tests and lung clearance disease, as demonstrated by CT scan imaging improved as well. HBOT improves the level of dissolved oxygen in the alveolar and inflammatory barriers, as well as the diffusion rate and distance of oxygen, by increasing the partial pressure of oxygen in the alveoli. In comparison to other oxygen delivery systems as nasal cannulas, face masks, invasive ventilation, non-invasive ventilation and ECMO, HBOT improves microcirculation and tissue oxygen delivery[34]. Patients with COVID-19 who were given HBO_2 had a better prognosis and avoided the need for mechanical breathing[39].

Previous COVID-19 trial[55] have shown that HBOT was initially successful and many of these experiments were undertaken when corticosteroids were not standard of treatment and earlier intubation was preferred. In hospitalized COVID-19 respiratory failure patients, adding HBOT to protocol therapy was connected to a decreased rate of intubation and mortality.

Conclusions

HBOT may be helpful as a source of oxygen when compared with other traditional oxygen therapy modalities for patients with COVID-19, especially if it is started at early stages. Moreover, it can avoid the need for mechanical ventilation and decrease the mortality rate. However, these observations were based on the results of case reports and case series studies. Thus, more clinical trials are required to confirm the effect of this intervention in COVID-19 patients in large sample size and to compare its efficacy in different stages.

Conflict of Interest

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