Review Article

International Journal of Research in Pharmaceutical Sciences

Published by JK Welfare & Pharmascope Foundation Journal Home Page: www.ijrps.com

Hyperbaric Oxygen Therapy and Its Suitability as an Adjuvant for Treatment of Covid-19 Patients: A Review

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Article History:

Received on: 01 Oct 2021
Revised on: 05 Nov 2021
Accepted on: 09 Nov 2021

Keywords:

Hyperbaric oxygen therapy,
Coronavirus,
COVID-19,
Therapeutic uses,
Hypoxia,
ARDS,
Cytokine Storm

Abstract

The outbreak of the SARS CoV2 'Coronavirus pandemic' is believed to have originated in Wuhan in 2019 as a zoonotic spread from bats to humans. It is a highly communicable infection-causing rapid human to human transmission of the virus by virtue of its infectious and pleomorphic nature. The virus has affected millions of people worldwide, with numbers still rising with each passing day. Depleting oxygen saturation levels is amongst the prime concerns in the majority of infected patients. Nasal prongs, face masks, mechanical ventilation and extracorporeal membrane (ECMO) are the commonly used modes of oxygen delivery in such patients. These methods though mostly successful, at times fail to restore the depleting oxygen levels to normal. Hyperbaric oxygen therapy (HBOT) involves the administration of 100% O2 in a special chamber whose pressure is maintained at a level greater than 1 ATP. The main purpose for raising the pressure within the chamber is that as the atmospheric pressure increases, the saturation levels of oxygen in the blood also increase, which eventually result in increased overall tissue oxygenation. This article provides a systematic and wholesome review on the basic principle of hyperbaric oxygen therapy, its effects on the body at a microscopic and macroscopic level, its various uses and its suitability as an adjuvant for the treatment of select COVID-19 infected patients.

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ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v12i4.4903

Production and Hosted by

IJRPS | www.ijrps.com

INTRODUCTION

The coronavirus pandemic is believed to have originated in Wuhan, causing a zoonotic spread from bats to humans. The SARS-Cov2 outbreak has infected millions of people across the globe. The presentation of symptoms usually begins after a typical incubation period of 2-14 days (Lauer *et al.*, 2020; Dawar and Jain, 2021). While the majority of the patients often remain asymptomatic or show mild flu-like symptoms such as fever, sore throat, cough, etc., a large fraction of patients with severe acute respiratory distress syndrome leading to multi-system organ failure and death have been reported (Shang *et al.*, 2020; CDC, 2021). Histological biopsy examinations of lung specimens have revealed gross bilateral diffuse alveolar damage with severe fibrosis. Interstitial mononuclear inflammatory infiltrates also been observed in liver and heart specimens (Yuki *et al.*, 2020). In such cases, supportive therapy with oxygen delivery systems such as nasal prongs, face masks, mechanical ventilation and extracorporeal membrane (ECMO) is used (Xu *et al.*, 2020; Senniappan *et al.*, 2020). These methods though mostly successful, at times fail to restore

the depleting oxygen levels to normal, which is one of the prime causes of the mortality associated with the Covid-19 infection. The use of hyperbaric oxygen therapy in such cases could be revolutionary, serving as a more effective and efficient oxygen delivery system, with super-added benefits such as reduction of over-expression of inflammatory mediators associated with cytokine storm and reduction in the overall viral load by the production of ROS.

A recent study conducted has reported the successful treatment of 20 covid positive patients with hyperbaric oxygen therapy (Zeng *et al.*, 2020). Hyperbaric oxygen therapy involves the administration of 100% O2 at elevated pressure. This ultimately increases alveolar PO2 and the overall tissue oxygenation and oxygen delivery thereby, overcoming one of the major obstacles in treating covid-19 patients.

Hyperbaric Oxygen Therapy

Working Principle

It can be said that the working principle of HBOT is derived from Henry's law. HBOT increases the partial pressure of oxygen in the lungs, which in turn increases the amount of oxygen dissolved in plasma.

HBOT is a form of treatment wherein a patient inspires high flow 100% O2 at a pressure higher than the sea level, i.e. more than 1 atp. The treatment is performed in a specialized chamber which may be either a monoplace chamber or multiplace chamber, depending on the number of people being treated at a particular time (Strauss, 2005). HBOT increases the alveolar partial pressure of oxygen and thus oxygen delivery, allowing for better tissue oxygenation. Inspiring 100% oxygen at sea level has a very minimal effect on the dissolved oxygen content in plasma, whereas the increase in the dissolved oxygen concentration of neatly 15 times has been reported at 3 ATP as compared to 1 ATP averaging an increase of 1.8 ml/dl for an increase of 1 ATP (McMahon *et al.*, 2002; Rao, 2008).

Effects on A Microscopic Level

Efficient oxygen delivery of oxygen to hypoxic and hypo-perfused tissues is the prime and most important effect of HBOT. The HBOT induced tissue oxygenation reverses the effects of hypoxia associated with inflammation by reducing the expression of adhesion molecules (ICAM-1, β2-INTEGRIN) on cells, thus reducing the activation of inflammatory cells (Rao, 2008). The chances of multi-organ dysfunction (MODS) associated with overexpression of TLR2 and TLR4 can be reduced by early initiation of HBOT as it reduces the expression of TLR2 and TLR4 (Perng *et al.*, 2004). The reduced inflammation results in reduced tissue oedema and improved overall tissue oxygenation (Memar *et al.*, 2019).

Additionally, HBOT induced oxidative stress is associated with the production of ROS, which have an antimicrobial activity which are of great benefit for treating severe covid-19 patients (Perng *et al.*, 2004).

Indications

The use of hyperbaric oxygen therapy has been a popular choice for the treatment of crush injuries, gangrene, osteoradionecrosis, necrotising skin infections, acute burns, diabetic foot wounds etc. (Halbach *et al.*, 2019). Its use is also implicated in other procedures such as management of embolisms, carbon monoxide poisoning, decompression sickness, arterial insufficiency, intracranial abscesses, severe anemia, etc. Recently its use has also been expanded to the field of plastic surgery owing to its good tissue healing properties, allowing surgeons to salvage compromised grafts with the prompt institution of HBOT (Shah, 2010; Kindwall *et al.*, 1991).

The use of HBOT is relatively noninvasive and causes less discomfort to the patient as compared to mechanical ventilation. HBOT has also improved oxygenation in patients with pneumonia when conventional therapies failed as it shows a reduction in the inflammatory response in aspiration pneumonitis (Zamboni *et al.*, 1996).

The Hb independent mechanism of oxygen transport may increase tissue oxygen delivery in Covid-19 patients. The same principle has been used previously to treat severely anemic Jehovah's Witness patients with HBO (Sahin *et al.*, 2011). Some of the conventional use of HBOT are as follows:

Osteomyelitis

Osteomyelitis is an infection involving the bone and its marrow contents (Salmen *et al.*, 2017). The infection is usually of bacterial origin. The condition usually responds well to treatment with antibiotics and surgical debridement. However, more severe cases are treated using HBOT. HBOT is usually conducted five to seven times per week, following wound debridement. 100% oxygen administration at 2.4-2.5 ATP is recommended. A total of 30 to 40 dives/sessions are conducted to obtain the desired results (Sivapathasundharam, 2009).

Osteoradionecrosis

Osteoradionecrosis involves infection of a recently irradiated bone. The condition is characterized by a triad of hypoxia, hypocellularity and hypovascu-

larity (Mader *et al.*, 1990). The most commonly followed testament is based on 'The Marx University of Miami Protocol', which includes a combination of antibiotics, surgical debridement and HBOT (Balaji and Balaji, 2019; Cronje, 1998). The treatment protocol involves 30 HBOT sessions depending on the responsiveness of the necrosed bone. The use of HBOT has shown drastic improvement and success in treating cases of ORN in more than 95% of the patients with predictable, functional and aesthetically acceptable outcomes (Balaji and Balaji, 2019; Marx *et al.*, 2019). The use of HBOT is nearly a standardised protocol for the treatment of osteoradionecrosis involving the mandible.

Gas Gangrene

Gas gangrene is caused by contamination by a wound caused by *Cl. perfringens*. The onset usually occurs within one to six hours of exposure, beginning with sudden localised pain followed by gradual discolouration and swelling of the affected area, ultimately causing bullae formation with putrid odour, loss of skin with blackish discolouration. If not recognised on time, it may require amputation of the limb or may even be fatal due to severe sepsis (McMahon *et al.*, 2002). The arrest of the spread of the aflatoxins produced is essential to control the infection. In addition to surgical debridement and administration of antibiotics, the use of HBOT becomes an important adjuvant to restore the arterial Po2levels and stop the spread of the toxins. Achieving P02 levels of 250 mm Hg is necessary to stop alpha-toxin production (Kindwall *et al.*, 1991).

Necrotizing fascitits

Necrotizing fascitits is an acute, potentially life-threatening infection that causes ischemic necrosis involving the superficial and deep dermal layers of the skin that is usually associated with infection of the wound by the necrotising bacteria - group A, C or G beta-haemolytic Streptococci (Lauer *et al.*, 2020; Kindwall *et al.*, 1991). Staphylococcus aureus infection in association with streptococcal infection may also occur at times, this is known as Meleney's synergistic gangrene

It is a rapidly progressing infection that manifests initially in the form of localized pain, swelling, fever and malaise. Vesicle and bullae formation takes place as the infection progresses further, involving deeper layers of the skin, eventually drying out and showing a clear region discoloration.

Treatment focuses on high dose antibiotics and surgical wound debridement. The use of HBOT has proven to show great success in multiple reported studies for the management of necrotising fasciitis. The current accepted and followed treatment protocol includes 100% O2, at 2-2.5 atp, for 90 minutes, twice a day for the first week or till there is no evidence of extension of the infection, along with regular wound debridement (Yang *et al.*, 2015).

Healing of Grafts and Wounds

The success of graft depends largely on the blood supply on the recipient site disruption of proper blood supply due to venous congestion, ischemia, infection, or arterial occlusion may at times occur, which compromises the graft (Halbach *et al.*, 2019). Compromised tissue grafts may be successfully salvaged with the prompt institution of HBOT (Lauer *et al.*, 2020; Kindwall *et al.*, 1991). The HBOT treatment protocol followed is 100% O2, 2-2.5 atpm for 90 minutes twice a day for the initial few days, following which treatment may be conducted once a day till desired results are achieved.

Preparation of the recipient site usually requires 20 HBOT cycles, followed by an additional 20 cycles following the placement of a graft onto the recipient site (Lauer *et al.*, 2020; Kindwall *et al.*, 1991).

The principle of HBOT in promoting arterial oxygenation has been employed for the treatment of compromised wounds, including diabetic foot wounds, as reported by multiple studies (Yang *et al.*, 2015).

All wounds are accepted to be hypoxic in nature, with the rate of healing being oxygen-dependent (Zeng *et al.*, 2020). As the level of infection rises, the tissue hypoxia increases (Lauer *et al.*, 2020). The rate of normal wound healing has been known to be oxygen-dependent. Angiogenesis, fibroblast migration, collagen deposition are oxygen-sensitive mechanisms that are required for wound healing. Using HBO increases the arterial Po2, thereby improving wound healing and promoting epithelization.

Diabetic Foot Wounds

The first clinical trial favouring HBOT for the treatment of diabetic foot wounds was conducted over 20 years ago (Broussard, 2004). Since then, HBOT has been recognised as a popular and effective treatment option with several randomised and non randomised clinical trials conducted over the years. A clinical trial conducted in the 1900s by Löndahl *et al.* (2010) was a double-blinded trial involving 16 non-diabetic patients who reported nono schematic leg ulcers. The trial concluded that the administration of HBOT drastically reduced the size of leg ulcers, proposing that the use of HBOT could greatly improve wound healing in diabetic foot wounds (Memar *et al.*, 2019).

HBOT reveres tissue hypoxia caused due to increased bacterial perfusion and necrosis, promotes fibroblast proliferation and collagen production, reduced the level of inflammation by down regulating the level of cytokines production and enhances the level of angiogenesis, thereby aiding healing by improving tissue repair and regeneration. Tissue regeneration (Baroni *et al.*, 1987; Gill and Bell, 2004). Amputation of diabetic foot wounds is a common practice in order to salvage the remaining limb and prevent the infection from spreading further. However, the use of HBOT has drastically decreased the need for amputation in such cases.

Hyperbaric oxygen therapy (HBOT) has been promoted as an effective treatment for diabetic foot wounds, and the first controlled trial for this indication was reported over 20 years ago HBOT on improving wound tissue hypoxia, enhancing perfusion, reducing edema, downregulating inflammatory cytokines, promoting fibroblast proliferation, collagen production, and angiogenesis make it a useful adjunct in clinical practice for "problem wounds," such as diabetic foot ulcers (Broussard, 2004; Baroni *et al.*, 1987; Gill and Bell, 2004). These beneficial effects, although requiring expensive technology, might powerfully reduce the risk of lower-extremity amputation in diabetic patients with foot wounds. Several randomized and non-randomized trials have been conducted demonstrating the effectiveness of HBOT in treating diabetic foot wounds, making it an important enterprise. A double-blinded randomized controlled trial conducted in the 1900s conducted by Löndahl *et al.* (2010) demonstrated a study of 16 nondiabetic patients with a nonischemic chronic leg ulcer that HBOT significantly reduced the size of the wounds during a six week observation period (Barnes, 2006; Abidia *et al.*, 2003; Löndahl *et al.*, 2010). This evidence allows the conclusion of the fact that the use of HBOT can greatly benefit the treatment of diabetic foot wounds, especially in cases that do not respond to other forms of treatment.

Carbon Monoxide Poisoning

Inhalation of high levels of carbon monoxide causes displacement of oxygen from the haemoglobin molecules to form carboxyhemoglobin, as a result, the amount of oxygen delivered to the tissues is reduced with an increase in the levels of carbon monoxide in the bloodstream. The use of hyperbaric oxygen therapy causes rapid displacement of the carbon monoxide molecules from haemoglobin and, in turn, generates normal oxyhemoglobin in the bloodstream (Hammarlund and Sundberg, 1994). The oxygen delivery to the tissue is also increased by the oxygen that is dissolved in the plasma, inducing faster recovery from the ischemic environment created. Additionally, the institution of HBOT reduces the adherence of neutrophils on the damaged endothelium of the blood vessels in the brain, which in turn reduces tissue edema and lipid peroxidation. The extra oxygen that is delivered to the tissue also helps to restore the oxidative phosphorylation in the mitochondria, which is paramount for the normal functioning and survival of neurons.

The COVID -19 Infection Cycle

The SARS-Cov2 is a highly contagious virus that spreads chiefly from the inhalation of infected respiratory droplets. There is usually an incubation period of 2-14 days before the symptoms become evident. It is self-limiting and mostly lasts for 10-14 days. However, new data suggests that the infection could still persist up to 21-28 days. Currently, the infectivity value of SARS-CoV-2 is estimated to be nearly 2-3, which is significantly higher in comparison to the values of the Spanish flu (R0 value - 0.9-2.1) (CDC, 2021; Yuki *et al.*, 2020). Symptoms may include loss of taste, loss of smell, malaise, febrile, dry cough, dyspnea, chills, muscle pain and loss of appetite etc. (Shang *et al.*, 2020). While the majority of the patients develop mild symptoms or remain asymptomatic, severe cases often result in MSOF leading to death.

Computed Tomography chest scans commonly demonstrate bilateral ground-glass opacities (Zeng *et al.*, 2020). Additionally, histological examination of lung specimens have revealed extensive damage due to cellular fibromyxoid exudates. Interstitial mononuclear inflammatory infiltrates also been observed in the liver and the heart specimens.

The infection commences of the virus with its attachment to specific ACE 2 receptors located on the host cell that are maximally present in the lungs (Xu *et al.*, 2020). The virus enters the cell via endocytosis and initiates the release of mature virions, which attack the host cells. These are phagocytosed macrophages. This, in turn stimulates T-cell immunity. The secreted viral proteins such as ORF3 and ORF10 cause the release of porphyrin molecules by attacking the beta haemoglobin chain, making the haemoglobin-oxygen binding inefficient (Xu *et al.*, 2020).

The severe symptoms are also associated with an increased level of cytokines in the body - TNF-alpha, IL-6, IL10, IL-8, GCSF and MCP1. IL-8 is an important chemoattractant for neutrophils and T cells which cause injury to the lung tissues resembling ARDS. Endothelial injury and thrombosis are correlated

with the elevated D-Dimer levels in covid positive patients (CDC, 2021).

So far, the use of conventional supportive oxygen therapy with nasal prongs, face masks and mechanical ventilation and extracorporeal membrane (ECMO) for more severe cases is used. These methods though mostly successful, at times fail to restore the depleting oxygen levels to normal (Xu *et al.*, 2020).

Implications of HBOT for The Treatment of COVID-19 Patients

Depleting oxygen levels is one of the major concerns in COVID-19 patients. The hypoxic condition created within the body may cause irreversible tissue damage, which may ultimately lead to multi-system organ failure and death (Buboltz and Robins, 2017).

At present, there is no definitive treatment protocol that has been devised for covid-infected patients, a multidisciplinary approach including suitable medications such as antipyretics, antiviral drugs, multivitamin supplements etc., are used depending on the presentation of the patient keeping in mind the preexisting comorbidities. Various adjuvant therapy approaches are often required during and after the infection, such as antithrombotics and antiplatelet drugs in patients depicting symptoms of thromboembolism and coagulopathy (Williams and Davis, 2020; Costanzo *et al.*, 2020), iron depletion therapy (Wool and Miller, 2021). Amongst these, the use of hyperbaric oxygen therapy is a relatively upcoming approach (Perricone *et al.*, 2020).

The use of HBOT dates back to the 1900s during the era of the Spanish flu. Dr Orville Cunningham successfully used HBOT to treat critically ill patients (Rao, 2008). Additionally, it was also demonstrated by Haldane that the use of pressurised O2 chambers may aid the treatment of carbon monoxide poisoning by enhancing tissue oxygenation.

Today the use of HBOT has been proposed as a supportive strategy to improve oxygenation in COVID-19 patients by many physicians as it is known to increase tissue oxygenation by increasing the amount of dissolved oxygen in plasma, thereby improving and aiding cell metabolism and functions, ultimately promoting tissue repair. The use of HBOT effectively declines the level of tissue inflammation and thus counteracts the ill-effects of cytokine storm in COVID-19 by reducing the expression of adhesion molecules ICAM1, β2 INTEGRIN on cells. This decreases the activation of inflammatory cells, which in turn reduces tissue oedema and improves overall tissue oxygenation (Rao, 2008; Memar *et al.*, 2019).

Additionally, HBOT induced oxidative stress proposes an antimicrobial activity with the production of reactive oxygen species (ROS), this helps lower the viral load in the body, thereby reducing the chances of multi-system organ failure and death (Perng *et al.*, 2004).

Various studies have shown that using HBOT as an oxygen delivery system is more effective than the use of nasal cannulas, facemasks, mechanical ventilation etc.

A study published by Zhong X, showed improvement of hypoxic states in a patient with severe covid pneumonia, with P02 levels running around 32 mmhg with the administration of HBOT at 2.0 APT, with the total treatment time lasting 95 minutes. The outcome revealed improved tissue hypoxia with an overall increase in oxygen saturation levels, improved appetite and lung functions (Shang *et al.*, 2020).

Another study published by Thibodeaux K reported the use of HBOT in a group of five COVID-19 patients with tachypnoea and desaturation. An average of five HBOT dives at 2 atp of 90 minutes each were provided.

As a result, mechanical intubation and ventilation were prevented in all five patients who additionally showed a decrease in inflammatory markers (D-dimer) (Zhong *et al.*, 2020).

A recent control study of 20 Covid-19 patients conducted at Winthrop Hospital, New York, suggested that the use of HBOT in such covid -19 patients with respiratory distress has been proven to be safe with a lower mortality rate when compared to the propensity-matched control group. Each patient was treated with roughly five HBOT cycles at 2 ATP, for 90 minutes each. The subdistribution hazard ratios were 0.37 for inpatient mortality (p=0.14) and 0.26 for mechanical ventilation (p=0.046) when compared to the patients treated with HBOT (Gorenstein *et al.*, 2020). It was also reported by Guo *et al.* (2020) that the application of HBOT in COVID-19 infected patients improved oxygen saturation levels, leucocyte count and D-dimer levels. Chest CT scans revealed improvement in covid - induced lung pathology (Thibodeaux *et al.*, 2020) [Table 1]. Though the current data presented is limited, the possibility of using HBOT as a standardized approach in treating select covid-19 infected patients with respiratory distress should be considered.

To summarise, the benefits proposed by the use of HBOT for treatment of covid-19 patients include:-

Table 1: Comparative analogy on various HBOT trials conducted for the treatment of covid-19 patients

First Author / Organization	Number of patients	Age Group (Years)	Presenting condition	HBOT Treatment	Outcome
(Zhong *et al.*, 2020)	1	69	P02 32 mmhg, severe covid pneumonia hypoxia	8 cycles, 95 minutes total treatment time 100% 200 kPa	Improved hypoxia and P02 levels. Improved lung functions and appetite. (Zhong *et al.*, 2020; Shang *et al.*, 2020).
(Thibodeaux *et al.*, 2020)	5	40-65	Reducing oxygen saturation levels with increased demand	5 dives, 90 minutes each, 100% O2, 2.0 ATP	mechanical intubation and ventilation was prevented in all patients. Decrease in inflammatory markers (D-dimer). Improved blood oxygen saturation levels and dyspneic states. (Thibodeaux *et al.*, 2020)
Gorenstein SA/ Winthrop Hospital New York	20	30-80	Increased O2 Requirement, Dyspnoea	5 dives. 90 minutes each, 100% O2, 2.0 ATP	The sub-distribution hazard ratios were 0.37 for inpatient mortality (p=0.14) and 0.26 for mechanical ventilation (p=0.046) when compared to the patients treated with HBOT (Gorenstein *et al.*, 2020)
(Guo *et al.*, 2020)	2	57, 64	P/F <300	7 Dives, 60 minutes each, 100% O2, 1.5 ATP	improved oxygen saturation levels, leucocyte count and D-dimer levels. Chest CT scans revealed improvement in covid - induced lung pathology. (Guo *et al.*, 2020)
(NSMCPT) Naval Specialty Medical Center Program Team	5	Not Disclosed	PaO2 37–78 mmHg (average) under 5–8 L/min O2	Not Disclosed	Improved dyspnoea and chest pain, decreased respiratory rate. SpO2 levels up to 95% at an average for all 5 patients (Yanagawa, 2021).

1. Efficient oxygen delivery to hypoxic and hypoperfused tissues
2. Mitigation of ill effects associated with over-regulation of inflammatory mediators
3. Antithrombotic effects
4. ROS- induced viral load reduction

Drawbacks and Complications

Like every therapy, the institution of hyperbaric oxygen therapy is also associated with some drawbacks and complications such as-

1. Lack of availability
2. Expensive
3. Not suitable for patients with claustrophobia (Johns Hopkins Medicine, 2021)
4. Not suitable for patients with recent ear surgery or injury (Johns Hopkins Medicine, 2021)
5. Not suitable for patients with conditions like collapsed lung (Johns Hopkins Medicine, 2021)
6. Pulmonary damage (Johns Hopkins Medicine, 2021)

7. Edema or bursting (rupture) of the middle ear, i.e. middle ear barotrauma (Johns Hopkins Medicine, 2021)
8. Sinus barotrauma (Skevas *et al.*, 2012)
9. Visionary changes, causing nearsightedness, or myopia - Hyperoxic Myopia (Nichols and Lambertsen, 1969; McMonnies, 2015)
10. Oxygen poisoning
11. Elevation of systolic and diastolic blood pressure in both hypertensive and non-hypertensive patients (Al-Waili *et al.*, 2006)
12. Dental barotrauma (Skevas *et al.*, 2012; Stoetzer *et al.*, 2012)
13. CNS oxygen toxicity and seizures (Heyboer-III *et al.*, 2017)

ABBREVIATIONS

HBOT- Hyperbaric Oxygen Therapy

O2- Oxygen

ATP - Atmospheric Pressure

P/A- Ratio of arterial to inspired oxygen

ROS - Reactive Oxygen Species

ORN - Osteoradionecrosis

NSMCPT -Naval Specialty Medical Center Program Team

ACE-2 - Angiotensin converting enzyme-2

ARDS- Adult respiratory distress syndrome

TRL - Toll-Like Receptors

Hb - Haemoglobin

CONCLUSION

With medical science and technology advancing with each passing day, newer methods and treatment strategies are coming up to fight the ongoing battle against the COVID-19 pandemic. While most of the patients remain asymptomatic or show only mild symptoms, a large number of cases have been reported where patients suffer from respiratory distress, which often leads to multisystem organ failure and death. Nasal prongs, face masks, mechanical ventilation and extracorporeal membrane (ECMO) are the most commonly used modes of oxygen delivery in such patients. However, these methods at times fail to restore the depleting oxygen levels back to normal. HBOT works by enhancing the total amount of oxygen in the blood and the overall tissue oxygenation, which is the key to overcoming respiratory distress. Though the current data available presented is limited, the possibility of using HBOT as a standardized approach in treating covid-19 infected patients with respiratory distress should be considered.

Conflict of Interest

The authors declare that they have no conflict of interest

Funding Support

The authors declare that they have no funding support for this study.

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