

Evidence Review for
HBO₂ Treatment of
COVID-19
Webinar



Abstracts



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Evidence Review for HBO₂ Treatment of COVID-19 Webinar

Abstract Papers

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Effects of volatile gaseous compounds induced by hyperbaric oxygen, in counteracting the SARS-CoV-2 virus in asymptomatic patients and SARS-CoV-2-positive patients with mild symptoms

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Hyperbaric oxygen (HBO₂) therapy will be provided at Centro Iperbarico in Ravenna, Italy, to patients as an adjunct to standard therapy for a cohort of 20 SARS-CoV-2-positive patients. These are asymptomatic patients or patients with mild symptoms who have nitric oxide synthase (NOS) genetic polymorphism and two or more comorbidities highly related to the reduced NO synthesis and the mortality rate in COVID-19.

In Italy, the median age of patients who died from COVID-19 is 20 years older than asymptomatic positive patients. In addition, 82% of deceased patients have concomitant diseases strongly correlated with NOS genetic polymorphism and reduced synthesis of NO.

HBO₂ therapy significantly increases the production of volatile gas compounds (VOCs) such as nitric oxide (NO), reactive oxygen species (ROS) and reactive nitrogen species (RNS), which in the laboratory has proven capable of inhibiting the replication of SARS-CoV-2. NO acts by reducing the palmitoylation of the spike glycoprotein (S) on the virus necessary to penetrate human cells. Furthermore, in the early stages of virus replication, NO reduces the reproduction of the genetic structure (viral RNA), altering proteins (cysteine proteases) encoded in the Orf1a genetic site of the SARS-CoV-1 virus, and supposedly it will act the same way on SARS-CoV-2.

HBO₂ upregulates the hypoxia-inducible factor, HIF (also induced by oxidative stress), which promotes the expression of human antiviral peptides: defensins and cathelicidins effective to block the coated, positive-sense single-stranded RNA virus (such as SARS-CoV-2).

The pilot study protocol includes five HBO₂ sessions of 76 minutes each, once a day, with control of the nasopharyngeal swab for SARS-CoV-2 after the third and fifth HBO₂ sessions. After the intervention portion of this study, a chart review will be performed to compare the outcomes of intervention patients versus patients who received standard of care (quarantine).

Efficacy and safety of hyperbaric oxygen for patients with COVID-19; rationale and protocol of the randomized controlled trial COVID-19-HBO₂

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Introduction: SARS-CoV-2 affects the innate immune response and activates an inflammatory cascade. Patients with risk factors such as diabetes and hypertension have increased risk of severe disease with inflammation out of control. Hyperbaric oxygen (HBO₂) has proven anti-inflammatory effects. The overall hypothesis to be evaluated is that HBO₂ may reduce mortality, increase hypoxia tolerance and prevent organ failure in patients with COVID-19 pneumonitis by reducing the inflammatory response. The primary objective is to evaluate if HBO reduces the number of ICU admissions compared to best practice for COVID-19. Main secondary objectives are to evaluate if HBO₂ reduces the load on ICU resources, morbidity and mortality in severe cases of COVID-19. Other objectives are to evaluate safety and evaluate and if HBO₂ mitigates the inflammatory reaction in COVID-19.

Materials and Methods: The trial *A Randomized, Controlled, Open-Label, Multicenter Clinical Trial to explore Safety and Efficacy of Hyperbaric Oxygen for preventing ICU admission, Morbidity and Mortality in Adult Patients With COVID-19* was initiated in Karlskrona, Sweden, on May 20, 2020. Additional centers are invited. An online eCRF (SmartTrial®) and online randomization tool (Randomize.NET) will be used.

Study design: Prospective randomized, open label, multicenter

Study population: 200 adults with moderately severe COVID-19 admitted to hospital and who require oxygen and have at least two risk factors for increased morbidity/mortality

Intervention: HBO₂ 1.6-2.4 ATA, 30-60 minutes, maximum five treatments within seven days

Control: Best practice for COVID-19 pneumonitis

Primary endpoint: ICU admission

Main secondary endpoints: 30-day mortality, time-to-intubation, time-to-ICU, mean change in inflammatory response

Results: *Ethics and dissemination* – The trial was approved by Swedish Ethical Review Authority (2020-01705) and Swedish Medicinal Products Agency (EudraCT 2020-001349-37). Results will be published in peer-reviewed scientific journals (OA). The Trial registration: NCT04327505.

Grants – Swedish Research Council.

Summary/Conclusion: A positive result from an RCT would make a strong argument in convincing health care systems to scale this treatment for general use against COVID-19 pneumonitis.

Hyperbaric oxygen therapy in preventing mechanical ventilation in COVID-19 patients: a multicenter case series

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Introduction: The highly contagious SARS-CoV-2 virus is responsible for the deaths of more than 100,000 Americans. Infected patients present with symptoms that range from minimal complaints to life-threatening respiratory failure. Elderly patients and those with comorbidities are at greatest risk for severe acute respiratory syndrome (SARS) requiring mechanical ventilation. Once on a ventilator mortality rates skyrocket. In April 2020 Dr. Thibodeaux treated five patients with severe COVID-19 at the Wound Treatment Center in Opelousas, Louisiana. The case series published in the *Journal of Wound Care* in May 2020 detailed the use of hyperbaric oxygen (HBO₂) therapy to reduce the need for mechanical ventilation. These results prompted further investigation.

Materials and Methods: An IRB-approved protocol and informed consent for the collection of de-identified information on COVID-19 patients treated with HBO₂ to reduce the need mechanical ventilation was provided to interested clinicians across the globe. Once registered on the SerenaGroup Research Foundation website, the investigational sites were provided with and trained to use a data collection app (Tissue Analytics, Baltimore, MD). Investigators obtained separate approval for the off-label use of HBO₂ therapy for COVID-19.

Results: Three sites have entered information on 12 patients treated with HBO₂ to prevent the need for mechanical ventilation. To date, 11/12 (91%) patients avoided mechanical ventilation. In addition, in the majority of patients, oxygen saturation increased, tachypnea resolved, and D-dimer levels and inflammatory markers fell. Ten sites have registered on the website. Further data is being uploaded at the time of this writing. No adverse events directly related to HBO₂ have been reported.

Summary/Conclusion: In this small sample of patients HBO₂ therapy appeared to reduce the need for mechanical ventilation in patients with severe COVID-19. Data collection is ongoing. However, the results thus far suggest that HBO₂ may be a safe and effective treatment of symptomatic COVID-19 disease.

Hyperbaric oxygen therapy for COVID-19 patients with respiratory distress: Treated cases versus propensity-matched controls

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Objective: Given the high mortality and prolonged duration of mechanical ventilation of COVID-19 patients, we evaluated the safety and efficacy of hyperbaric oxygen for COVID-19 patients with respiratory distress.

Methods: This was a single-center clinical trial of COVID-19 patients at NYU Winthrop Hospital from March 31 to April 28, 2020. Cases received hyperbaric oxygen therapy at 2.0 atmospheres of pressure in monoplace hyperbaric chambers for 90 minutes daily for a maximum of five total treatments. Controls were identified using propensity score matching among COVID-19 patients admitted during the same time period. Using competing-risks regression to perform a survival analysis, we studied our primary outcome of inpatient mortality and secondary outcome of mechanical ventilation.

Results: We treated 20 COVID-19 patients aged 30 to 79 with hyperbaric oxygen, with an oxygen requirement ranging from 2 to 15 liters on hospital days 0 to 14. Of these 20 patients, two (10%) were intubated and died, and none remain hospitalized. Among 60 propensity-matched controls based on age, sex, body mass index, coronary artery disease, troponin, D-dimer, hospital day, and oxygen requirement, 18 (30%) were intubated, 13 (22%) have died, and five (8%) remain hospitalized (two of whom are still on mechanical ventilation). Assuming, no further deaths or intubations among controls, we estimate that the adjusted subdistribution hazard ratios were 0.37 for inpatient mortality ($p=0.132$, 95% CI of 0.10 to 1.37) and 0.26 for mechanical ventilation ($p=0.046$, 95% CI of 0.07 to 0.98).

Conclusions: Though limited by its study design, our results demonstrate the safety and possible efficacy of hyperbaric oxygen among COVID-19 patients and strongly suggests the need for a well-designed multicenter randomized control trial.

Sounding the alarm: An unexpected hyperbaric emergency during the COVID-19 pandemic

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Case description: The impact of increased hospital burden due to COVID-19 extends even to outpatient “COVID-free” units and hospital-based hyperbaric programs not treating COVID populations. While the majority of discussion concerning the impact of COVID-19 is correctly focused on patient outcomes and the role of hyperbaric oxygen (HBO₂) in treatment – as well as staff/HBO₂ patient safety in terms of infection control when/where COVID patients are receiving HBO₂ treatment), there is a potential for an increased burden on bulk O₂ delivery systems that can impact hyperbaric programs. This includes monoplace and multiplace facilities and is a safety concern that is often not frequently drilled or seen. Incidents can occur when oxygen demand from the bulk O₂ delivery (LOX) system is greatly increased, such as in the case of hospitalized and critically ill patients during the COVID-19 pandemic. The author presents a case report outlining a recent high-pressure alarm experienced and resolved at Plainview Hospital’s Division of Advanced Wound Healing and Hyperbaric Medicine.

Intervention: Chamber operations were halted until O₂ pressure was satisfactorily controlled by high-pressure power washing of LOX vaporizers by engineering staff.

Outcome: Incoming O₂ pressure was restored; staff, including the hyperbaric safety director, gained understanding of LOX systems.

Discussion: The primary emphasis of this case is the importance of communication among hospital departments and leadership, the utilization of those resources, and the importance of interdisciplinary problem-solving.

The role of hyperbaric oxygen treatment for COVID-19

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Introduction: The recent COVID-19 pandemic produced extreme demands for hospitalizations and equipment, with depletion of critical care resources. Current therapies provide limited clinical relief, and a robust vaccination program is not yet available. Therefore, several empirical investigations were initiated with intermittent hyperbaric oxygen (HBO₂) therapy to overcome the relentless and progressive hypoxemia that is often refractory to maximal ventilator support of intubated patients. However, more recently, less severe patients at the edge of impending hypoxemia were exposed to HBO₂, which prevented intubation and obtaining the rapid resolution of symptoms. With this summary we illustrate the possible biological mechanisms of action of HBO₂ in COVID-19 patients.

Materials and Methods: We performed a scoping review, gathering the most valuable evidence supporting mechanisms of action of HBO₂ and possible overlaps with COVID-19 pathophysiology.

Results and Discussion: First, HBO₂ acts by increasing the amount of oxygen in the plasma and peripheral tissues. Possible direct effects of HBO₂ on viruses are still uncertain, but in COVID-19 patients, hyperoxia could mobilize stem cells, block the inflammatory cascade, interfere with interstitial fibrosis development in the lungs, delay the onset of severe interstitial pneumonia, and reduce the risk of multisystem organ failure due to an overall abated SARS-CoV-2 viral load. HBO₂ proved able to reduce interleukins levels, specifically of IL-1 beta, IL-6, IL-8, and TNF-alfa, all involved in the development of pulmonary fibrosis. Moreover, the increased production of nitrogen oxide during HBO₂ can increase vasodilation and reduce platelet activation, potentially hampering the procoagulant state encountered by COVID-19 patients. HBO₂ also seems to preserve the antioxidant capacity of lymphocytes, thus protecting the resilience of the immune system that is known to be impaired in COVID-19 cases. Potential, known adverse effects of

HBO₂ – such as oxygen pulmonary toxicity, hyperoxic seizures, or transient visual impairment – are preventable and rare at pressures currently used.

Conclusion: In this period it seems reasonable to take every possible method into account to take care of COVID-19 patients. Despite its possible beneficial effects, the role of HBO₂ in COVID-19 patients still needs to be demonstrated with properly designed trials. Therefore, when using HBO₂, clinicians should weigh possible benefits with potential damages and risks.