Hyperbaric Oxygen and COVID-19

Clinical trials registered on clinicaltrials.gov

1. Hyperbaric Oxygen (HBO_2) Therapy as a Treatment for COVID-19 Infection

(not yet recruiting) • (HBO_2 protocol not given)

Sponsor: Ochsner Health System, New Orleans, Louisiana ((NCT number): NCT04343183
Information provided by (Responsible Party)/PI: John Engle, Ochsner Health System

STUDY DESCRIPTION

Brief Summary: Patients who meet inclusion criteria will be randomized into treatment versus control group. Treatment groups will undergo hyperbaric oxygen (HBO_2) therapy (protocol not described) and compared to the control group.

Detailed Description: After enrollment, patients will be randomized into treatment versus control group. Both populations will receive the same inpatient medical treatment. All patients in the treatment group will undergo hyperbaric oxygen therapy under the same treatment protocol. After completion of the treatment protocol, specific study endpoints will be compared between the treatment and control groups.

STUDY DESIGN

Study type	Interventional (Clinical Trial)
Estimated enrollment	48 participants
Allocation	Randomized
Intervention model	Parallel assignment
Intervention model description	This study will utilize a single-center sequential two-parallel-group (HBO_2/standard care) randomized controlled design with two looks to allow for early stop due to clear benefit/harm.
Masking	Single (Outcomes Assessor)
Masking description	The biostatistician and radiologist will be blinded.
Estimated study start date	April 2020
Estimated study completion date	June 2020

OUTCOME MEASURES

Primary Outcome Measures

1. Decrease incidence of intubation by 30% or greater [time frame: one month];
   Compare rates of intubation between treatment and control groups

Secondary Outcome Measures

1. Decrease renal injury [time frame: one month];
   Measure glomerular filtration rate (GFR) and compare between treatment and control groups

ELIGIBILITY / INCLUSION CRITERIA

1. adult inpatients >18 years old (all sexes)
2. positive PCR COVID-19 testing
3. CT evidence of interstitial lung opacity
4. oxygen saturation <90% on room air
5. pO_2 = 55-70

EXCLUSION CRITERIA

1. increased oxygen requirements
2. hemodynamic instability (MAP<65)
3. bradycardia (HR <50)
4. history of seizure disorder
5. pneumothorax
6. GFR <30
7. hemodialysis
8. refractory anxiety/claustrophobia
9. current pregnancy
10. Uncorrectable hypoglycemia

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2. Hyperbaric Oxygen for COVID-19 Patients: NCT0433208

(Recruiting) • HBO_2 protocol as below • (HBO_2 2.0 ATA 1-5 treatments)

Sponsors and Collaborators: NYU Langone Health; NYU Winthrop Hospital
Information provided by (Responsible Party): NYU Langone Health

STUDY DESCRIPTION

Brief Summary: Hyperbaric oxygen (HBO_2) therapy treatment will be provided to patients as an adjunct to standard therapy for a cohort of 40 COVID19-positive patients with respiratory distress at NYU Winthrop Hospital. All patients prior to the clinical application of HBO_2 will be evaluated by the primary care team and hyperbaric physician. 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.

Detailed Description: This is a single-center prospective pilot cohort study to evaluate the safety and efficacy of hyperbaric oxygen (HBO_2) therapy as an emergency investigational device for treating patients with a novel coronavirus disease, COVID-19. Patients who meet inclusion criteria will be consented by the hyperbaric physician. They will then be transported from the ED or other unit to the hyperbaric unit while maintaining airborne precautions based on the most current hospital protocol. All study personnel will have proper PPE at all times. The patient will then be placed into the monoplace chamber and when the chamber door is closed the patient will remove any respiratory filter/mask that was placed. The patient will receive 90 minutes of hyperbaric oxygen at 2.0 ATA with or without air breaks per the hyperbaric physician. Upon completion of the treatment the patient will then return to the medical unit and continue all standard of care. Additional treatments (up to 5) can be given if warranted and agreed upon by the patient and all members of the team caring for the patient. 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.

STUDY DESIGN • OUTCOME MEASURES

Primary Outcome Measures

1. Mortality [time frame: duration of hospitalization: 5-7 days on average]

Secondary Outcome Measures

1. Days on invasive mechanical ventilation [time frame:: duration of hospitalization: 5-7 days on average]

ELIGIBILITY / INCLUSION CRITERIA

In order to be eligible to participate in this study an individual must meet all of the following criteria:

1. male or female, age >18 years
2. positive COVID-19 test
3. respiratory compromise defined by SpO_2 <93%
4. ability to sign informed consent

EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. pregnancy
2. untreated pneumothorax

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3. Management by Hyperbaric Oxygen Therapy of Patients With Hypoxaemic Pneumonia With COVID-19: NCT04344431 (Recruiting)

Sponsor: Direction Centrale du Service de Santé des Armées

STUDY DESCRIPTION

Brief Summary: Several patients with hypoxaemic SARS-CoV-2 pneumonia were able to benefit from hyperbaric oxygen (HBO_2) treatment in China. In a clinical case published in the *Chinese Journal of Hyperbaric Medicine*, treatment with repeated HBO_2 sessions prevented admission to intensive care unit with mechanical ventilation in a patient aged 69 who presented with signs of respiratory decompensation. HBO_2 can dramatically increase the amount of dissolved oxygen in the blood. HBO_2 not only promotes blood transport but also its tissue delivery. Furthermore, HBO_2 has specific immunomodulatory properties, both humoral and cellular, making it possible, for example, to reduce the intensity of the inflammatory response and to stimulate antioxidant defenses by repeating sessions. A virucidal capacity of HBO_2 therapy might also be involved.

Detailed Description: The main objective of this study is to assess the effectiveness of HBO_2 in addition to normal management over the period of normalization of the oxygen requirement (oxygen dependence) in patients with SAR-CoV-2 pneumonia not requiring invasive or non-invasive ventilation. It is a prospective, interventional, multicenter, controlled, randomized study. Patients admitted for SARS-CoV2 pneumonia in the COVID sector of the hospital who have oxygen-dependence criteria will be proposed for inclusion in accordance with the inclusion and non-inclusion criteria. Randomization will be carried out to determine the allocation in two groups: an HBO_2 group which will perform a daily session after checking for the absence of contraindication to HBO_2 and a non-HBO_2 control group with the same clinical criteri, but who will not benefit from HBO_2 sessions. In both groups standard continuous treatment with normobaric oxygen will be maintained.

STUDY DESIGN

Estimated enrollment	100 participants
Allocation	Randomized
Intervention model	Parallel assignment
Masking	Single (Outcomes Assessor)
Primary purpose	Treatment
Actual study start date	April 14, 2020
Estimated primary completion date	April 2021
Estimated study completion date	May 2021

OUTCOME MEASURES

Primary Outcome Measures

1. Time to normalize the oxygen requirement (oxygeno-dependence), i.e., allowing a pulse oximetry value in ambient air greater than or equal to 92% and / or arterial blood gas with a PaO_2 value greater than 60mmHg in ambient air

Secondary Outcome Measures

1. Days of hospitalization between the HBO_2 group and the control group
2. Number of days with oxygen need, taking into account the predictors of bad outcome
3. Oxygen flow values to obtain a saturation by pulse oximetry greater than or equal to 92% values between the HBO_2 group and the control group
4. Oxygen flow values to obtain a saturation by pulse oximetry greater than or equal to 92% between the HBO_2 group and the control group
5. Days on invasive mechanical ventilation
6. Mortality

ELIGIBILITY / INCLUSION CRITERIA

1. male or female, age ≥18 years
2. patient with oxygen dependence criterion: need to maintain an oxygen flow rate less than or equal to 6 liters / minute to obtain saturation by pulse oximetry (SpO_2) greater than or equal to 92% or arterial gas with value PaO_2 greater than 60mmHg
3. diagnostic confirmation of COVID-19 pneumonia

EXCLUSION CRITERIA

1. minor subject (age <18 years)
2. person unable to give consent
3. pregnancy
4. participating in another research
5. signs of respiratory decompensation requiring mechanical ventilation
6. diagnosis of pneumonia with SARS-CoV-2 not confirmed
7. oxygen dependence criterion exceeded, i.e., need to maintain an oxygen flow rate greater than or equal to 6 liters / minute to obtain saturation by pulse oximetry (SpO_2) greater than or equal to 92% or arterial gas with value of PaO_2 greater than 60mmHg
8. inability to maintain the prolonged sitting position (at least 2 hours)
9. subject with contraindications to HBO_2 therapy

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4. Safety and Efficacy of Hyperbaric Oxygen for ARDS in Patients With COVID-19

(HBO_2 protocol 2.4 bar (2.4 ATA), 30 minutes (excluding compression/recompression-maximum 5 treatments over 7 days)

Karolinska University Hospital

Collaborators: Karolinska Institutet; University of California San Diego; Blekinge County Council Hospital

STUDY DESCRIPTION

Brief Summary: Mortality rates in patients who develop ARDS is extremely high, 61.5-90%, almost double the mortality of ARDS of any cause. ARDS associated with COVID-19 is associated with pulmonary edema, rapidly progressing respiratory failure and fibrosis. The mechanism behind the rapid progress is still an enigma, but theories have evolved around severe inflammatory involvement with a cytokine storm. HBO_2 significantly reduces inflammatory cytokines and edema.

Detailed Description: Mortality rates have been reported as high as 90% in patients developing ARDS in early reports and more recent reports have reported overall 28-day mortality rates of 61.5% in ICU patients with acute respiratory illness. ARDS associated with COVID-19 differs from other ARDS, with rapidly progressing respiratory failure and fibrosis. Macrophage activation is involved early and cytokine modulators such as interleukin-6 (IL-6) inhibitors have been tried in experimental settings but no proper clinical trials have proven positive outcome. Hyperbaric oxygen (HBO_2) significantly reduces inflammatory cytokines including IL-1β, IL-6 and TNF-α through several transcription factors regulating inflammation, including hypoxia inducible factor 1 (HIF-1), Nrf2 and NFkB.

STUDY DESIGN

Study type	Interventional (Clinical Trial)
Estimated enrollment	200 participants
Allocation	Randomized
Intervention model	Parallel Assignment
Intervention model description	Randomized controlled, open label, multicenter
Masking	None (Open-Label)
Primary purpose	Treatment
Estimated study start date	April 25, 2020
Estimated primary completion date	October 31, 2021
Estimated study completion date	December 31, 2022

PRIMARY OUTCOME MEASURES

1. PO_2/FiO_2 (safety) oxygen requirement (arterial blood gas (pO_2)
2. Fraction of inspired oxygen within 1 hour before and after HBO_2 and 6 hours after each HBO_2 treatment. PO_2/FiO_2 (efficacy)
3. Oxygen requirement (arterial blood gas (pO_2) and recorded fraction of inspired oxygen) At baseline, daily for 7 days, Day 14 and Day 30 (or last day in hospital if patient is discharged earlier or at withdrawal) irrespective of HBO_2 treatments.
4. National early warning score mean NEWS at baseline, within 1 hour before and after and 6 hours after HBO_2, daily for 7 days, Day 14 and Day 30 (or last day in hospital if patient is discharged earlier, or at withdrawal) irrespective of HBO_2 treatments.
5. Immunological response: Measurement baseline, daily for 7 days, Day 14, Day 30 (or last day in ICU if patient has left ICU earlier, or at withdrawal)
   a. Complete blood cell count including WBC count + differential
   b. C-reactive protein
   c. Procalcitonin
   d. Cytokines including but not limited to IL-6
6. Mechanical ventilation: Days free of invasive mechanical ventilation

SECONDARY OUTCOME MEASURES

1. Adverse events, including SAE – serious adverse events
2. Serious ADR – serious adverse drug reaction
3. Oxygen dose: Mean oxygen dose calculated as oxygen tolerance units (OTU)
4. Imaging, including pulmonary CT (low-dose CT), chest X-ray and chest ultrasound
5. Secondary infections
6. Mortality
7. ICU-free days
8. ICU mortality: Mortality for any cause in ICU (% of patients admitted to ICU)
9. Hospital mortality: Mortality of any cause in Hospital
10. Micro RNA plasma (biomarker-change in expression of micro RNA in plasma (qPCR) and micro RNA/RNA PBMC baseline, Day 3, Day 5, Day 7, Day 14, Day 30. First 20 patients.
11. Immunological response: Baseline, Day 3, Day 5, Day 7. In first 20 patients Cytokines extended, including (IL-1β, IL-2, IL-6, IL33 and TNFα). Lymphocyte profile flow cytometry with identification of monocyte/ lymphocyte subsets including but not limited to CD3+/CD4+/CD8+ monocyte proliferation markers
12. Viral load (quantitative PCR) (Baseline, Day 7, Day 14, Day 30)

OTHER OUTCOME MEASURES

1. Staff safety – Serious and all adverse events in staff associated with treatment of COVID patients
2. HBO_2 feasibility
   a. Number of HBO_2 treatments given/planned first 10 days
   b. Received HBO_2 treatment within 24 hours of enrolment (Yes/No)

ELIGIBILITY / INCLUSION CRITERIA

1. age 18-90 years, both genders
2. patient meets ARDS criteria (Berlin definition) and needs intubation, ventilator-assisted or ECMO-assisted treatment within 7 days of admission to hospital
3. suspected or verified COVID-19 infection
4. at least one risk factor for increased mortality in COVID-19: currently published, e.g., smoking, hypertension, diabetes, cardiovascular disease
5. documented informed consent according to ICH-GCP and national regulations

EXCLUSION CRITERIA

1. ARDS with etiology other than COVID
2. known pregnancy or positive pregnancy test in women
3. patients with previous lung fibrosis
4. CT- or spirometry-verified severe COPD with emphysema
5. contraindication for HBO_2 according to local guidelines
6. do not resuscitate (DNR) or other restrictions in escalation of level of care

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5. Hyperbaric Oxygen Therapy Effect in COVID-19 RCT (HBOTCOVID19) (HBOTCOVID19) NCT04358926 (not yet recruiting) (HBO_2 protocol not specified; 8 sessions of HBO_2 vs. 8 sessions of normobaric O_2 in chamber over 4 days

Sponsor: Assaf-Harofeh Medical Center
Information provided by (Responsible Party): Assaf-Harofeh Medical Center

STUDY DESCRIPTION

The 2019-20 coronavirus disease caused by COVID-19 is an ongoing pandemic. So far no specific treatment has proven efficacy. Recent case series reported the use of hyperbaric oxygen (HBO_2) therapy on 5 severe COVID-19 patients who developed respiratory insufficiency. HBO_2 mechanisms of tissue oxygenation and anti-inflammatory effect may explain these findings. The purpose of the current study is the evaluate the efficacy of HBO_2 therapy in moderate-severe COVID-19 patients in a randomized controlled manner.

STUDY DESIGN

Study type	Interventional (Clinical Trial)
Estimated enrollment	30 participants
Allocation	Randomized
Intervention model	Parallel assignment
Intervention model description	Randomized controlled, double-blinded
Masking	Double (Participant, Outcomes Assessor)

OUTCOME MEASURES

Primary Outcome Measures

1. PaO_2/FiO_2: 1 day and 7 days after the last intervention session. Oxygenation index of the lungs calculated PaO_2 measured in the blood divided by the inhaled FiO_2.
2. SpO_2: One hour prior to and after every intervention session, 1 day and 7 days after the last intervention session. Oxygen saturation measured in %.
3. NEWS Score: One hour prior to and after every intervention session, 1 day and 7 days after the last intervention session national early warning score (NEWS) calculated by the patient's vitals and condition.
4. Inflammation level: 1 day and 7 days after the last intervention session including white blood cell count, CRP level, ESR and cytokines: IL-1, IL-2, IL-6, IL-10, TNF-α, procalcitonin, ferritin.

Secondary Outcome Measures

1. Symptoms level: 1 day and 7 days after the last intervention session. Patient's reported symptoms including cough, dyspnea, etc.
2. Average oxygen supply per day: 1 day and 7 days after the last intervention. Oxygen amount supplied measured in IU.
3. Viral load: 1 day and 7 days after the last intervention session. Quantitative measurement of viral load in the blood using quantitative RT-PCR.
4. Chest X-ray changes: 1 day and 7 days after the last intervention session. Chest xray changes evaluated qualitatively and quantitatively.
5. Number of patients with IgG seroconversion: 1 day and 7 days after the last intervention session. Number of patients who developed SARS-CoV-2 IgG antibodies.
6. Number of patients with IgM seroconversion: 1 day and 7 days after the last intervention. Number of patients who developed SARS-CoV-2 IgM antibodies.
7. FEV1/FVC: 1 day and 7 days after the last intervention session. Pulmonary function tests performed bedside.
8. Time to symptoms recovery within 30 days. Measured time patient suffered symptoms until complete recovery.
9. Number of patients who required invasive ventilation within 30 days.

10. Time to negative virus PCR within 30 days. The measured time until the patient had two negative SARS-CoV-2 PCRs.
11. Mortality rate within 30 days.
12. Number of barotrauma events within 7 days after the last session.
13. The number of adverse events in each arm.

INCLUSION CRITERIA

1. adults (age 18 or older)
2. male and female
3. positive SARS-CoV-2 RT-PCR
4. at least one risk factor for bad prognosis of COVID-19: hypertension, diabetes mellitus, ischemic heart disease, smoking, age >50, etc.
5. respiratory insufficiency: room air SpO_2 <94% or PaO_2/FiO_2 <300mmHg
6. ability to sign an informed consent

Exclusion Criteria

- negative SARS-CoV-2 RT-PCR
- HBO_2 therapy contraindication: pneumothorax, pneumomediastinum, claustrophobia, ear/sinus disease, known chronic pulmonary disease such as severe emphysema or known pulmonary bullae.
- pregnancy
- inability to sign an informed consent

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6. The Compassionate Use of Hyperbaric Oxygen Therapy in the Treatment of COVID-19 NCT04386265

Sponsor: SerenaGroup, Inc. (Collaborator: The Wound Treatment Center)
Information provided by (Responsible Party): SerenaGroup, Inc.

STUDY DESCRIPTION

This is an observational patient registry of COVID-19 patients treated with HBO_2 therapy. The retrospective analysis will focus on the reduction in need for mechanical ventilation in COVID-19 patients. The information will be gathered prospectively. Data will be collected from the patients' medical record, including medical notes and data recorded into the study database.

STUDY DESIGN

Study type	Observational (Patient Registry)
Estimated enrollment	100 participants
Observational model	Case-only
Time perspective	Prospective
Target follow-Up duration:	2 years
Estimated study start date:	May 11, 2020
Estimated primary completion date:	May 11, 2022
Estimated study completion date:	May 11, 2022

OUTCOME MEASURES

Primary Outcome Measures

1. Gather information on patients treated with hyperbaric oxygen therapy. Collect information on the reduction in need for mechanical ventilation in COVID-19 patients (time frame 24 months).

Secondary Outcome Measures

1. Gather information on adverse events by following adverse events associated with the treatment of COVID-19 related to HBO_2 therapy (time frame 24 months).

ELIGIBILITY / INCLUSION CRITERIA

- Study population: Adult patients with COVID-19
- Ages eligible for study: 18 Years and older (Adult, Older Adult)
- Sexes eligible for study: All
- Sampling method: Non-probability sample
- A signed and dated informed consent form for the off-label use of hyperbaric oxygen therapy specific to the institution where treatment is rendered
- Subject is willing and able to comply with instructions and scheduled visits

EXCLUSION CRITERIA

- The subject has other concurrent conditions that in the opinion of the investigator may compromise patient safety
- The patient has an untreated pneumothorax

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