Safety and efficacy of Low-pressure hyperbaric oxygenation in severe COVID-19 patients: a study protocol of an open-label randomised controlled trial

Bo Yang (stemothyroid@live.com)
Naval medical center of PLA  https://orcid.org/0000-0003-0680-1469
Zeping Jiang
Naval medical center of PLA
Yuting Liu
Naval medical center of PLA
Lan Zhou
Naval medical center of PLA
Lingling Ding
Naval medical center of PLA
Lingling Zhu
Naval medical center of PLA
Yang Liu
Naval medical center of PLA
Nanmei Liu
Naval medical center of PLA

Research Article

Keywords: COVID-19, Low-pressure hyperbaric oxygenation, randomized controlled trial

Posted Date: August 28th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3211348/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

**Introduction:** COVID-19 pandemic remains an acute global emergency. The situation was especially worrying in mainland China. However, paxlovid shortage led to the underuse of recommended antivirus treatment. Hyperbaric oxygen (HBO) therapy could increase SpO\(_2\) in COVID-19 patients with severe hypoxemia. The prior trials suggested this potential effectiveness while the study design and sample size may not be sufficient in illustrating the effectiveness and safety of HBOT. Therefore, we designed the current protocol to examine the hypothesis that HBO may improve disease severity and decrease mortality after infection.

**Methods and analysis:** This study is an open-label randomised controlled trial. A total of 40 COVID-19 patients with disease progression scale 5 or higher will be randomly assigned to control group or HBO therapy (HBOT) group. The control group will receive usual care according to the latest guidelines of the CDC for COVID-19. Besides the usual care, the patients in HBOT group will receive seven low-pressure (1.6 ATA) HBOT session in consecutive 7 days. The primary outcome was defined as WHO clinical progression scale difference before and after the seven-day study. Secondary outcomes include pulse oximetry value at the end of study; duration of hospitalization; newly developed COVID-related symptoms or comorbidity; serum inflammatory biomarks; chest imagining improvement; and HBOT associated adverse events.

**Ethics and dissemination:** Ethics approval has been obtained from the Institution Review Board of Naval medical center of PLA (No: 2023010601). Written informed consent will be obtained from each subject. The findings of this study will be actively disseminated through scientific publications and conference presentations.

**Trial registration number:** ChiCTR2300070759

**INTRODUCTION**

Although WHO declare that COVID-19 no longer constitutes a public health emergency of international concern. COVID-19 pandemic remains a worrying situation in mainland China. Millions of people have been infected at the end of 2022 and the covid-19 patients filled up emergency rooms and hospitals. According to the CDC guideline, certain high-risk patients are eligible for nirmatrelvir-ritonavir[1], while paxlovid shortage in the local marketplace lead to the underuse of recommended antivirus treatment. In this case, other options are applied or even tested for improvement of disease severity.

Hyperbaric oxygen (HBO) therapy could increase SpO\(_2\) in COVID-19 patients with severe hypoxemia[2]. In our previous report in 2020, we experimentally apply HBO in COVID-19 patient (alpha variant), whose hypoxemia could not be corrected with standard mechanical ventilation. Eight HBO sessions buy the time of recovery and the disease course was reversed [3]. After the experimental treatment, several clinical trials have showed that HBO may improve oxygenation in COVID-19 patients with hypoxemia.[4–6].
The prior trials suggested the potential effectiveness while the study design and sample size may not be sufficient in illustrating the effectiveness and safety of HBOT. Therefore, we designed the current study to test the hypothesis that HBO may improve disease severity and decrease mortality after COVID-19 infection.

**METHODS AND ANALYSIS**

The protocol is reported according to the recommendations for interventional trials (SPIRIT) guidelines (Fig. 1–2).[7]

**Patient and public involvement**

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Subjects inclusion**

Inclusion criteria are as follows: 1) male or female patients over 18 years of age; 2) confirmed diagnosis of COVID-19 by PCR assay using nasal swab sample; 3) WHO clinical progression scale is 5 or higher [8]. Exclusion criteria are as follows: 1) patients unable to give consent; 2) pregnant women; 3) having any contraindications for HBO therapy (such as acute respiratory distress syndrome (ARDS), claustrophobia, severe chronic obstructive pulmonary disease, emphysema, air cysts or bullae and untreated pneumothorax); 4) vital signs are expected unstable during the therapy session.

**Randomisation and treatment allocation**

Subjects are randomized in a 1:1 ratio to undergo HBOT or usual care. Group assignments are produced with a computer software generated randomization sequence. The assignments are then placed in opaque envelops. After confirming that the eligibility of a certain patient, the subject is enrolled if the informed consent was given. Randomization will be conducted by opening the prepared envelop. The group assignment is open-labeled to subjects, clinicians and study personnel. Demographic and baseline characteristics will be collected for the enrolled subjects.

**Study interventions**

**Control group**

For patients assigned to the control group, usual care according to the latest guidelines of the CDC for COVID-19 was given, which include oxygenation/ ventilatory support; NSAIDs; low-dose dexamethasone; baricitinib; empiric antibiotic therapy and chronic medications.

**HBOT group**

For patients assigned to the HBOT group, besides the usual care in control group, seven low-pressure HBOT session will be conduct in consecutive 7 days. HBO therapy administered once daily using
Revitalair technology (1.6 ATA) with an inspired fraction close to 100% of oxygen for 60 min session. As preventive measures, chambers were cleaned with ultraviolet light for 30 min between patients. The selection of equipment with a pressure of 1.6 ATA was based on several benefits: the possibility of transporting the single-patient equipment and ease of handling and disinfection, the reduced likelihood of lung damage, and easiness of installation (important in the context of the pandemic).

**Primary outcome**

The primary outcome was defined as WHO clinical progression scale difference before and after the seven-day study.

**Secondary outcome**

Secondary outcomes include 1) pulse oximetry value at the end of study; 2) duration of hospitalization; 3) newly developed COVID-related symptoms or comorbidity; 4) serum inflammatory biomarks (CRP, PCT, IL-6 and ferritin); and 5) chest imaging improvement. The safety endpoint was to evaluate the adverse events during and post HBO treatment. Adverse events related to HBO therapy were recorded, including the presence of ear pain, ear obstruction, barotrauma, or other symptoms.

**Sample size estimation**

A power calculation was performed in which, a sample size of 16 subjects per group was required to achieve 80% power with a type I error rate of 0.05 (two-tailed) [9]. A final plan to enroll 40 subjects into this trial was decided to account for a 20% dropout rate. Sample size calculation was done in PASS 15.

**Statistical analysis principles**

Data will be analysed with an intention-to-treat approach. Continuous variables are expressed as medians (interquartile ranges, IQRs) or means ± standard deviations (SDs) and were compared using the Wilcoxon rank-sum test or Student's t test. Categorical variables are expressed as counts (%) and were compared using the $\chi^2$ test or Fisher’s exact test.

**ETHICS AND DISSEMINATION**

The Ethics Committee of the Naval medical center of PLA has reviewed and approved this protocol (approval no. 2023010601). This study will adhere to the principles of the Declaration of Helsinki. The study will be conducted at the Naval medical center of PLA.

Each participant will voluntarily sign a written informed consent form. Each study participant will be assigned an identification number throughout the trial to assure confidentiality. The results of this study will be published in open-access and peer-reviewed journals and presented at relevant conferences.

**DISCUSSION**

COVID-19 pandemic remains a worrying situation in mainland China. Due to the lack of the more effective mRNA vaccine, Chinese population is more vulnerable to the disease. Millions of people have
been infected at the end of 2022. A new wave of cases is peaking in the summer of 2023.

The current RCT will be the first to evaluate the hypothesis that HBOT (1.6 ATA) may improve disease severity and decrease mortality after COVID-19 infection in Chinese population. The HBO treatment has been acknowledged as a safe and efficient therapy for COVID-19 patients, providing a resolution to low oxygen levels and alleviating inflammation [9,10]. Additionally, having contracted the virus causes the body to enter a hypermetabolic state, which leads to a higher demand for oxygen and ultimately results in the deprivation of tissue oxygen. HBO can mitigate this condition [9,11,12]. A clinical trial conducted by Mariana et al. observed COVID-19 patients who were experiencing severe hypoxemia (SpO₂ of ≤ 90% despite receiving oxygen supplementation). These patients were administered HBO at a pressure of 1.45 ATA for 90 minutes. The outcomes showed that the group who received the HBO treatment saw an improvement in their low oxygen levels within three days as opposed to the control group who saw improvement after nine days [13]. Another cohort study was conducted on COVID-19 patients who had moderate to serious hypoxemia and PaO₂ was less than or equal to 80 mmHg. These patients were given HBO for 30 to 45 minutes at a rate of 2.0 ATA. The results of this study showed that after only three sessions of HBO, patients had increased their PaO₂ levels to 90 mmHg [13]. However, the sample size of the study was limited, and the readouts did not included the WHO clinical progression scale. Through the current study, we hope to identify the effectiveness of HBOT in severe COVID-19 patients. Our results may provide valuable information for developing a novel treatment method for improving disease severity and decreasing mortality.

Declarations

Trial status:

Participant recruitment is in progress. the date recruitment began was 2023-01-10. The approximate date when recruitment will be completed 2023-12-31. The study was started according to the protocol in its first version dated Jan. 05, 2023.

Ethics approval and consent to participate

This study was approved by the Institution Review Board of Naval medical center of PLA (No: 2023010601). Written informed consent will be obtained from each subject.

Consent for publication

Written informed consent was obtained from the patients for publication of this manuscript and accompanying images.

Availability of data and material

The trial dataset generated and/or analyzed during the current study will not be publicly available due to ethical and data privacy issues in health care but will be partly available from the corresponding author or
sponsor upon reasonable request. The CRF templates for both study arms may be delivered upon reasonable request.

Competing interests

None.

funding statement

This study is supported by Shanghai Talent Development Fund (2020071), the Excellent Talent Engineering Fund of Naval Medical Center of PLA (21TPZY3201).

Authors' contributions

YL and NL conceptualized and designed the study. BY, ZJ, and YL is the principal investigator of the study. LZ, LD, LLZ drafted the manuscript that was reviewed and edited by BY and ZJ. All authors read and approved the final manuscript.

References


Figures
COVID-19 patients with WHO clinical progression scale is 5 or higher

screening and baseline assessment

assessment for eligibility

informed consent

randomisation control group intervention: conventional care

randomisation HBOT group intervention: conventional care+ HBOT

primary outcome: WHO clinical progression scale difference before and after the seven-day study

Secondary outcomes:
1) pulse oximetry value at the end of study;
2) duration of hospitalization;
3) newly developed COVID-related symptoms or comorbidity;
4) serum inflammatory biomarkers;
5) chest imaging improvement.

data analysis and statistics

**Figure 1**

flow chart of the study design
### Figure 2

content for the schedule of enrolment, interventions, and assessments.

### Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.
• SPIRITChecklistdownload8Jan13.doc