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|  | **Investigation of utility of Hyperbaric Oxygen Treatment (HBOT) for Long-COVID syndrome**Keyline divider beneath title**Principal Investigators:**Dr Susannah Sherlock, Dept of Anaesthesia Royal Brisbane and Women’s Hospital, Burns, Trauma and Critical Care Research Centre (BTCCRC), Wesley Hyperbaric Unit, University of Queensland (UQ), Brisbane.Honorary Adjunct Associate Prof Graeme Kay, Director, Wesley Hyperbaric.Prof André Van Zundert, Prof and Chairman Division of Anaesthesia, UQ, Chair UQ ‘Burns, Trauma & Critical Care Research Centre’, Chair RBWH University of Queensland ‘Centre of Excellence & Innovation in Anaesthesia’, Brisbane, QLD.**Associate Investigators:** **Dr Yena Hwang, Wesley Hyperbaric VMO****Dr Louisa Kippin, Wesley Hyperbaric VMO** |

# Introduction

This study is a controlled trial to test the effectiveness and utility of using hyperbaric oxygen treatment (HBOT) in the management of Long-COVID syndrome.

#### Background

The pandemic announced in March 2020 by the World Health Organisation (WHO) due to the SARS-CoV-2 virus acutely infected millions of people worldwide and was responsible for over six million two hundred thousand deaths by April 2022. The chronic syndrome of disability left in its wake is a further concern which many researchers are currently trying to understand.

WHO recently defined Long-COVID syndrome or Post COVID-19 as “the illness that occurs in people who have a history of probable or confirmed SARS CoV-2 infection; usually within three months from the onset of COVID-19, with symptoms and effects that last for at least two months. The symptoms and effects of post COVID-19 condition cannot be explained by an alternative diagnosis”.[1]

It is estimated to affect as many as 10 – 20 % of patients who become infected with the SARS CoV-2 virus. While age, comorbid medical conditions, and COVID-19 disease severity are risk factors, young and previously healthy individuals with mild COVID-19 are also at risk.[2] Those who have had more time bed-ridden are more likely to have longer term mental morbidity including depression.[3]

The predominant symptoms are fatigue and dyspnoea but cognitive disorders, chronic muscle and joint pain, loss of smell and taste, hair loss, cardiac and gastrointestinal dysfunction are all well recognised. Less common symptoms including visual impairment, ear pain and chills have also been described. Debility and loss of quality of life are becoming an increasing societal concern.[4]

#### Rationale for the use of HBOT

Hyperbaric Oxygen Treatment (HBOT) is the provision of 100 % oxygen at an atmospheric pressure greater than 1 atmospheric pressure (ATA).[5] The chamber is compressed with air and the oxygen is given by a hood or a sealed face mask to prevent oxygen build up within the chamber. Each patient is on an independent breathing source and exhaust gasses are scavenged to outside. This allows very high partial pressures of oxygen in the blood with saturation of haemoglobin and dissolved oxygen content levels reaching high levels. Mitochondrial function improves after HBOT and has several effects on oxidative stress with increased reactive oxidative stress at higher levels of exposure. HBOT induces transcription factors and gene expression evoking anti-oxidant enzymatic activity especially via the nuclear factor erythroid 2 related factor 2 (Nrf2) and also vascular endothelial growth factor (VEGF).[6]

HBOT protocols cause a large oxygen fluctuation (from high during treatment to low after treatment) which is thought to provoke a hypoxic signal without actual hypoxia. This activates cellular transcription factors and improves mitochondrial activity. Activation of hypoxia inducing factor (HIF) and SIRT1 (a class III histone deacetylase) improves neuronal survival, cell proliferation and modulates the stress response. Mitochondrial function is important in immune cells to drive the anti inflammatory response. Improved mitochondrial function has been linked to cognitive improvement.[7]

Reduced lung diffusion has been a commonly described pathological response to the SARS-CoV-2 virus which persists in half of survivors. Oxygen is the substrate for mitochondria to produce energy via metabolic pathways. Defects in gas exchange have been shown to persist in long term follow up studies in patients with long-COVID. Brain structural and metabolic dysfunction have also been demonstrated in COVID-19 patients who have persistent cognitive impairment.[8]

In addition, immune responses are thought to contribute to damaged organs due to exaggerated inflammatory responses. Both T cells and B cells are thought to be activated for a prolonged period causing further inflammation and tissue damage. Increased inflammatory biomarkers have been shown in patients with persistent symptoms, including C-reactive protein (CRP) and D-dimer.[9, 10]

HBOT has well established therapeutic benefits in hypoxic tissues and in reducing the inflammatory response which occurs as a result of embolism and radiation injury. It has been utilised in a number of conditions where anti-inflammatory tissue effects and modulation of inflammatory response have been shown to occur.

#### 1.3 Current evidence

Thus far, only one case report and one retrospective case series have been published on the use of HBOT in long-COVID. Both had methodological flaws but showed statistical and clinical improvement in patients.[11, 12] There are two trials registered with the clinical trials network which are currently investigating HBOT in long-COVID; one in Denmark and one in the United States. Both are small and still recruiting.

The United Kingdom’s guideline on management of long-COVID based upon the NICE (National Institute for Health and Care Excellence), SIGN (Scottish Intercollegiate Guidelines Network) and RCGP (Royal College of General Practitioners) guidelines is brief. There are currently no treatment options available to Long-COVID sufferers other than advice and supportive strategies.[13]

#### 1.4 Need for a clinical trial

The rationale for the trial is as follows:

* Long-COVID is expected to affect millions of people who survived the acute SARS-CoV-2 infection potentially causing a new health pandemic.
* Long-COVID in children has an estimated incidence of 8% and the health implications remain unknown in the next generation.
* The European Observatory on Health Systems and Policies (hosted by the WHO) recommendation for a multi-disciplinary approach for management strategies to be developed.[14]
* Economic burden expected from long term reduced productivity, lockdowns and sick leave.

#### 1.5 Clinical significance

The SARS-CoV-2 virus is an ever-changing virus with many unknown long-term effects. Any promising treatment that may reduce the burden of disease and the impact (both psychosociological and economical) should be investigated to assess utility. If HBOT proves effective, the number of units in Australia may need to be increased as currently there are only a few medically accredited units with low capacity.

2.0 Study Design

#### 2.1 Aim

To conduct a randomised controlled trial to determine if HBOT improves cognition, symptoms of fatigue, and pulmonary gas exchange in patients with Long-COVID.

#### **2.2 Hypothesis**

HBOT reduces inflammatory markers, improves pulmonary gas exchange, neurocognition and symptoms of fatigue by modulating the inflammatory response.

#### **2.3 Design**

This will be a controlled trial to replicate the results in a similar, non-controlled, small study conducted by the UK NHS (National Health Service). There will be randomisation (1:1) to either the HBOT arm of treatment or no HBOT (control). The control group will be supportive care only as per current treatment guidelines.

Recruitment

This study will be communicated by the focus groups who we have approached already. We have had support for the concept of this trial and already have a waiting list of people who are interested once HREC review has been completed. There are a number of Facebook groups and participant support groups who are happy to promote the trial to those with the condition.

We will not be directly approaching participants but will rely on communication via our website, support groups and media coverage to allow participants to approach the research group at the Wesley Hyperbaric Unit.

**CONSORT HBOT for Long-COVID Flow Diagram**

Assessed for eligibility (n= 100)

## Enrollment

Excluded (n= )

  Not meeting inclusion criteria (n= )

  Declined to participate (n= )

  Other reasons (n= )

consented (n= )

## Allocation

Allocated to control . No HBOT (n= )

Allocated to HBOT (n= )

## Follow-Up

Lost to follow-up (give reasons) (n= )

Discontinued intervention (give reasons) (n= )

Lost to follow-up (give reasons) (n= )

Discontinued intervention (give reasons) (n= )

## Analysis

Analysed (n= )
 Excluded from analysis (give reasons) (n= )

Analysed (n= )
 Excluded from analysis (give reasons) (n= )

3.0 Study Outcomes

#### 3.1 Primary Outcome

Improvement in neurocognitive score.

#### 3.2 Secondary Outcomes

1. Improvement in pulmonary function measured via spirometry FEV1, % predicted FVC, % predicted peak expiratory flow (PEF)
2. Improvement in fatigue score
3. Improvement in I min sit to stand testing
4. Side effects of HBOT: middle ear barotrauma (MEBT) / refractory changes / major events

# 4.0 Study Participants

#### 4.1 Study Setting

This study will be conducted in the chief investigator’s private practice rooms (initial consultation, examination, consent discussion and randomisation); treatment will occur at the Wesley Hyperbaric Centre for those who have consented and been randomised to HBOT.

#### 4.2 Inclusion Criteria

Inclusion Criteria:

* 18 to 65-year old
* COVID-19 at least 12 weeks prior, +PCR test/ RAT and/or documented clinical symptoms
* Active lifestyle before contracting COVID-19

#### Exclusion Criteria

Exclusion Criteria:

* Pregnant or lactating women
* Individuals that are unable walk or get in and out of bed by themselves unaided
* Inability to provide written informed consent
* Inability or unwillingness to adhere to 10 HBOT treatment sessions over a 2 to 3 week- time period or to complete questionnaires/testing
* Claustrophobia and inability to enter the hyperbaric chamber for session
* Inability to effectively equalise the middle ear during ambient pressure changes. History of tympanic membrane perforation, head and neck surgery with compromised Eustachian tube function, including tracheostomy, mastoidectomy, middle ear surgical procedures and cochlear implants
* Contraindication to HBOT such as cardiac or respiratory contraindication, bleomycin, spherocytosis or pulmonary fibrosis
* Involved in another clinical trial that does not allow enrolment in other clinical trials

5.0 Study Interventions

#### **5.1 Study treatment regimens**

* 5.1.1 Control group (no HBOT)
* 5.1.2 Hyperbaric oxygen treatment group (HBOT)

Daily compression at 2.4 ATA in a multiplace or monoplace chamber according to unit protocols; 90 mins breathing 100% oxygen at treatment pressure (Mon to Fri) for 10 treatments.

#### 5.2 Withdrawal of study treatment

Following randomisation, every effort will be made to ensure participants continue to receive the allocated treatment protocol. Unless a participant chooses to withdraw consent to participate in the study, they will be included in the analysis on an intention-to-treat basis.

Withdrawal may occur for any of the following reasons:

* Withdrawal of consent to be in the study.
* Inability to compress (with or without necessitation of grommets).
* Intercurrent illness which necessitates withdrawal.
* Other treatment proven to be effective which is openly available.
* Adverse or serious adverse events related to treatment irrespective of group allocation.

#### 5.3 Blinding

This is a single blinded study as patients will be aware of treatment group as will treating clinicians. The statistician will be blinded to the study allocation group.

#### 5.4 Safety considerations

There is no additional risk to patients from participating in this study other than the risk of HBOT which is considered a safe treatment for many conditions with low risk of side effects.

HBOT is a safe procedure with a low incidence of serious side effects.[15] CNS oxygen toxicity is the most common of the serious side effects (risk of seizure 1.2 per 5000 at 2.4 ATA) and usually has no long-term morbidity associated with it. Common, non-serious side effects include barotrauma (most often in the tympanic membrane, up to 20% in some reports) and reversible myopia which will be discussed as part of the routine consent process.

# 6.0 Study Assessments

6.1 Screening

#### 6.3 Baseline

#### Neurocognition, fatigue score, 1 min sit to stand test and pulmonary function tests .

Participants will be screened by senior hyperbaric physicians as defined by AS4774.2 for eligibility in the study when they present to them for management using tools to assess fitness for hyperbaric developed specifically to assist them. This may be the rostered on call hyperbaric physician.

#### 6.2 Randomisation

Participants meeting all inclusion criteria and none of the exclusion criteria will be consented and then be randomised. This will be by envelopes which assign them by a random allocation sequence to a group; HBOT treatment group or no treatment. Randomisation is 1:1. blood testing will be collected at presentation by the hyperbaric consultant / hyperbaric nurse prior to HBOT.

#### 6.4 Schedule of assessments

Testing will be repeated 3 months after treatment group completion.

#### 6.5 Follow up at 6 months

Repeat fatigue score on telephone survey.

# 7.0 Safety Monitoring and reporting

#### 7.1 Adverse events

Any adverse event thought to be related to study assignment will be reported to the CI within 7 days.

7.1.1 Serious adverse events (SAEs)

These are defined as any event which:

* Results in death
* Is life threatening
* Requires admission to hospital
* Results in significant disability

7.1.2 Suspected unexpected serious adverse reactions (SUSARS)

Defined as unexpected event whose nature, severity, specificity or outcome is not consistent with a hyperbaric oxygen reaction.

7.1.3 Reporting SAEs and SUSARs

All SAEs and SUSARs will be reported to the HREC by the Chief Investigator within 24 hours.

#### 7.2 Data and safety monitoring committee (DSMC)

An independent DSMC will be formed to monitor recruitment, data storage, monitor follow up and SAEs and SUSARs. The Chief Investigator is responsible for reporting to the DSMC.

All adverse reactions (both SAEs and SUSARs) will be promptly reported to the DSMC within 24 hours of the event. The report will contain patient name, trial identifier, details of event and outcome.

#### 7.3 Study termination

The study may be terminated at any time after consultation with the DSMC. Local Human Research Ethics Committee (HREC) will be promptly informed and the Chief Investigator will provide details outlining the reasons. Funding bodies (if any) will also be informed.

# 8.0 Ethics

#### 8.1 Ethical Principles

This study will abide by the ethical principles of the Declaration of Helsinki and the National Health and Medical Research Council (NHMRC) National Statement on ethical conduct in human research.

#### 8.2 HREC

This study will be reviewed by the University of Queensland HREC. Any amendment or protocol modification will have HREC approval prior to implementation unless the change is necessary to eliminate hazard to a patient, in which case, the HREC and DSMC should be notified as soon as possible hereafter.

The Chief Investigator will provide progress reports, adverse events reports and other documentation as directed by the HREC in accordance with their guidelines. Copies of all correspondence pertaining to HREC locally or satellite sites will be kept by the Chief Investigator.

#### 8.3 PICF and procedures

This study assesses the effectiveness of one treatment strategy. Participants not given hyperbaric oxygen (the control group) will be treated at the discretion of their GP. Participants who are enrolled will be offered a PICF (attached) to inform them of the nature of the study. This form will also have been assessed and approved by the HREC.

#### 8.4 Privacy

All patient data will remain confidential and be stored in accordance with the local site regulations.

# 9.0 Data collection and Management

#### 9.1 Record retention

The Chief Investigator will ensure all data is retained for at least 15 years after the completion of the study. This will be stored on a secure hard drive in a secure location on site at Wesley Hyperbaric Centre. The Chief Investigator must inform the HREC prior to any planned or accidental record destruction.

# 10.0 Quality Control

#### 10.1 Responsibilities of Chief Investigator

The Chief Investigator is responsible for the overall running of the study in accordance with the protocol and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline for Good Clinical Practice. Responsibilities include:

* Provision of reliable, legible data as requested by HREC or DMSC in a timely fashion.
* Allow access of representatives to source documents

#### 10.2 Responsibilities of Co- Investigators

* Provision of SADRs and ADRs to Chief Investigator.
* Protocol adherence.
* Local HREC reports as required.
* Local data accuracy and storage.

#### 10.3 Management of protocol deviations

A protocol deviation may be an omission, addition or change to the protocol. No deliberate protocol deviations should occur unless pertaining to patient safety. All protocol deviations need to be recorded and sent to the Chief Investigator who will also inform the DSMC and HREC.

# 11.0 Statistical methods

11.1 Power calculation

This is not possible given the paucity of data and changing variants of the virus. It is noted that a small study of 10 patients showed a statistical improvement in neurocognitive testing following HBOT. We have decided to recruit 30 participants as this is a feasible number.

11.2 Analysis Plan

The effectiveness of the intervention (HBOT) will be evaluated by an intention-to-treat analysis of all eligible patients who are randomised. A biostatistician will formulate the appropriate statistical testing to compare the outcomes between the two groups.

11.3 Interim analyses

An interim analysis will be performed after 50% of patients (50 patients) have been recruited and completed 6-month follow-up.

# 12.0 Publication

It is envisioned that this trial will be of interest, whatever the outcome, and be publishable.

# 13.0 Proposed project timeline

This study should take 6 months to complete

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