Hyperbaric oxygen therapy for patients with COVID-19

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Dr Cannellotto and colleagues have published a prospective, multi-centred, open-label randomised controlled study of hyperbaric oxygen (HBO_2) as an adjuvant treatment for patients with COVID-19 who have severe hypoxemia. The study included 40 patients, 20 in the HBO_2 treatment arm and 20 in a control (no HBO_2) arm who were unable to achieve an oxygen saturation of 90% despite oxygen supplementation. In the current era—both in terms of well conducted research and especially given the COVID-19 pandemic—this is a deceptively difficult challenge to overcome. HBO research is often hobbled by preconceptions about its utility and the costs of performing it appropriately. I would also point out that this was done in Argentina even though the majority of patients with COVID-19, if not the majority of HBO_2 chambers themselves, lie outside of that country. This group of interested, committed clinicians were trying to improve the care of their patients with COVID-19 in a time of a pandemic and also managed to write up their work on behalf of all. Bravo.

The study by Cannellotto and colleagues[1] balanced many factors relating to COVID-19 so as to be maximally safe for the enroled participants. The authors selected a very low treatment pressure, 1.45 ATA, and by doing so attempted to minimise any haemodynamic risks for the enroled patients. Those less familiar with HBO_2 should know that 1.4 ATA is the minimum therapeutic level for clinical HBO_2 use in the USA[2] and lower therapeutic pressures have been proposed for other clinical conditions, but such low treatment pressures remain a subject for further study. As the applied pressure surrounding the body is increased, higher levels of tissue oxygenation are achieved, but other changes in tissue responses, whole body cardiovascular effects and host inflammatory responses also occur, and some provoke haemodynamic changes that can increase risk for patients.[3] Researchers are attempting to determine what might be optimal pressures for the treatment of COVID-19 and other conditions.[4]

The authors also chose a more cost effective, lighter weight model of an $HB0_2$ chamber (Revitalair technology), which is not a completely rigid chamber and does not appear to go much above 1.4 ATA. This may have assisted in running the study at three sites. Presumably should HBO_2 be found to be more efficacious than previously assumed, lower cost, lighter chambers for HBO_2 delivery would allow more patients to access treatments.

The study was stopped after a preliminary analysis suggested that HBO_2 therapy was safe and those receiving it had faster times to reduced oxygen needs. This meant that the study only included 40 patients where originally it intended to include 80 patients, which potentially prevented observation of significant differences in long-term outcomes. I think it is notable that the authors stopped the study when they felt adequate safety had been demonstrated, even when continuing the study might have contributed to further statistically significant effects.

While the authors showed a clear benefit in terms of fewer days to improvement in oxygen requirements, it is important to recognise some aspects of recruitment that could suggest which patients this form of HBO_2 therapy might apply to. The authors excluded patients if they could not remain in a seated position for more than 2 hours, although online depictions of the use of Revitalair chambers seem to demonstrate patients being in semi-recumbent or beach chair positions. In addition, the participants needed to be able to tolerate being off oxygen for 5 min for assessment of their room air saturations. Although this was not stated as an inclusion criterion, the authors do not tell us if patients decompensated during this time and thus were not able to be included in the study. Both of these aspects could mean that the patients in the study were not necessarily representative of all patients admitted to hospital with COVID-19 who remained hypoxic on oxygen therapy. Also none of the patients received antivirals or monoclonal antibody preparations, which might also suggest less severe infection (unless these treatments were not available in the hospitals). What might have been useful would have been to obtain the clinical parameters of the patients with COVID-19 who were in hospital at the time of the study to understand the spectrum of illness of the included patients.

One enrolment criterion was SpO2 <90% despite oxygen supplementation. A wide variety of oxygen supplementation methods have been used due to clinical parameters and patients' tolerance of these methods. More details about the methods of oxygenation used in these patients would be helpful to interpret the study results. Perhaps with larger numbers, we could determine which oxygen therapies (or failure thereof) are associated with improvement with HBO_2 therapy.

Finally, it would be helpful to understand the time frames from presentation of symptoms to diagnosis to need for oxygen or hospitalisation to enrolment? Additionally, if patients receiving HBO_2 returned to normal oxygen levels more quickly, did this achieve any cost savings in terms of earlier discharges or conservation of overall oxygen use?

Nevertheless, the data from this study are consistent with other recent work involving HBO_2 therapy in patients with COVID-19. These studies have shown that patients begin treatment with very high respiratory rates and raised inflammatory markers, both of which seem to decrease with HBO_2.[5 6] during and even after HBO therapy periods. HBO has a direct effect on oxygen absorption and its delivery to the body's tissues, and therefore increases oxygen saturations. The mechanism by which this treatment decreases inflammation is still being worked out.

The study failed to find changes in acute respiratory distress syndrome, mechanical ventilation or death, but this is probably because of the small numbers in the study, and the selection of possibly a less critical cohort of patients. Larger studies must start with smaller studies. Alternative therapies must be considered. Could five to seven 90 min HBO treatments when amortised for each patient's treatment course compete with other advanced therapies, such as antiviral based therapies for costs, logistical feasibility, value and efficacy?

As we all look to improve our global capabilities to combat the effects of COVID-19, this study demonstrates the value of looking to make the most of available resources to properly evaluate novel treatment modalities such as

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a lower cost, portable, lower pressure HBO_2 to make a clinical impact on this pandemic.[4]

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