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Hyperbaric oxygen as an adjuvant treatment for patients with COVID-19 severe hypoxaemia: a randomised controlled trial

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ABSTRACT

Background Hyperbaric oxygen (HBO₂) therapy has been proposed to treat hypoxaemia and reduce inflammation in COVID-19. Our objective was to analyse safety and efficacy of HBO₂ in treatment of hypoxaemia in patients with COVID-19 and evaluate time to hypoxaemia correction.

Methods This was a multicentre, open-label randomised controlled trial conducted in Buenos Aires, Argentina, between July and November 2020. Patients with COVID-19 and severe hypoxaemia (SpO₂ ≤90% despite oxygen supplementation) were assigned to receive either HBO₂ treatment or the standard treatment for respiratory symptoms for 7 days. HBO₂ treatment was planned for ≥5 sessions (1/day) for 90 min at 1.45 atmosphere absolute (ATA). Outcomes were time to normalise oxygen requirement to SpO₂ ≥93%, need for mechanical respiratory assistance, development of acute respiratory distress syndrome and mortality within 30 days. A sample size of 80 patients was estimated, with a planned interim analysis after determining outcomes on 50% of patients.

Results The trial was stopped after the interim analysis. 40 patients were randomised, 20 in each group, age was 55.2±9.2 years. At admission, frequent symptoms were dyspnoea, fever and odynophagia; SpO₂ was 85.1%±4.3% for the whole group. Patients in the treatment group received an average of 6.2±1.2 HBO₂ sessions. Time to correct hypoxaemia was shorter in treatment group versus control group; median 3 days (IQR 1.0–4.5) versus median 9 days (IQR 5.5–12.5), respectively (p<0.010). OR for recovery from hypoxaemia in the HBO₂ group at day 3 compared with the control group was 23.2 (95% CI 1.6 to 329.6; p=0.001). Treatment had no statistically significant effect on acute respiratory distress syndrome, mechanical ventilation or death within 30 days after admission.

Conclusion Our findings support the safety and efficacy of HBO₂ in the treatment of COVID-19 and severe hypoxaemia.

Trial registration number NCT04477954.

INTRODUCTION

The COVID-19 pandemic triggered a public health crisis worldwide. The most problematic clinical features of this disease are hypoxaemia and systemic

Key messages

What is already known on this subject

- ▶ Hypoxaemia in COVID-19 has a pathophysiology not yet fully understood. Many patients have required invasive and expensive treatments for hypoxaemia. Limited literature has suggested that hyperbaric oxygen is a safe and effective oxygenation method for patients with COVID-19, but well-designed studies are needed.
- ▶ Prior case studies and non-randomised clinical trials have suggested the utility of hyperbaric oxygen for hospitalised patients with COVID-19.

What this study adds

- ▶ In this multicentre randomised controlled trial of hyperbaric oxygen therapy at 1.45 atmospheres of pressure among patients with COVID-19, hypoxia was resolved in significantly shorter time in those receiving HBO₂ therapy than control patients.
- ▶ Findings suggest hyperbaric oxygen is safe and effective in the treatment of severe hypoxaemia in patients with COVID-19.

hypoxia, produced by ventilation-perfusion mismatch and alveolar inflammation.¹ Hypoxaemia has been independently associated with in-hospital mortality in patients with COVID-19; in moderate to critically ill patients, oxygen saturation (SpO₂) of more than 90% with oxygen supplementation indicate a very high likelihood of survival, while values below 90%, despite normobaric oxygen supplementation, have been associated with a high mortality risk.² Impaired oxygen diffusion leads to a drop in oxygen levels, which produces hypoxaemia and further inflammation.^{3–5} In severe pneumonia caused by COVID-19, impaired oxygen diffusion leads to hypoxaemia and lower level of oxygen-haemoglobin saturation.^{3–5}

Oxygen administered at higher pressure increases the partial pressure of oxygen in the haematoalveolar exchange, increasing gas diffusion through an altered alveolar membrane which, under the hyperbaric environment, produces a larger amount of



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dissolved oxygen in plasma and tissues.⁶ Moreover, hyperbaric hyperoxia has been associated with reduction of the inflammatory response.⁷ Hypoxaemia correction and hyperoxia generation could trigger an anti-inflammatory effect that, in turn, could lead to a clinical improvement in patients with hypoxaemic severe pneumonia associated with COVID-19.^{5,8} In case studies, HBO₂ therapy has proved to be effective and safe in patients with COVID-19 pneumonia.^{9,10} In patients that received HBO₂ therapy, SpO₂ increased, tachypnoea resolved and inflammatory markers decreased.^{10,11} Randomised controlled trials investigating HBO₂ therapy in patients with COVID-19 have not been published so far.

When receiving HBO₂ treatment, patients breathe oxygen inside a chamber at a pressure higher than the atmospheric pressure at sea level; for clinical use, pressure is usually greater than 1.45 ATA.¹² HBO₂ therapy at medium pressure (below 2 ATA) has shown that it is neurologically safer than treatment at higher pressures.^{12–15} However, as the increased pressure of HBO₂ therapy may exacerbate an acute lung injury or induce pulmonary oedema among patients with COVID-19, potential complications must be assessed.¹¹ The objective of this study was to analyse the safety and efficacy of HBO₂ treatment in patients with COVID-19 with severe hypoxaemia in the reduction of time for recovery from hypoxaemia (defined as SatO₂ ≤93%). Also, the study evaluated if HBO₂ treatment decreased progression to respiratory distress, mechanical ventilation requirements and mortality.

MATERIALS AND METHODS

This was a multicentre randomised controlled clinical trial of patients with COVID-19 performed at three public hospitals in Buenos Aires, Argentina. When the study was registered, two patients had been enrolled.

Sample size calculation

A sample size of 80 patients (40 in each group) was calculated with a reduction of at least 60% in the time needed to reach SpO₂ of 93% (with the app epi <https://www.openepi.com/Sample-Size/SSCohort.htm>). The sample size was based on a reduction of ≥60% in the time needed to reach SpO₂ of 93%, using an alpha error of 0.05% and 80% power. This gave a sample size of 80 patients, 40 in each group.

Patient selection

Inclusion criteria were as follows: patients in emergency department (ED) or intensive care unit, over 18 years of age (all sexes), with confirmed diagnosis of COVID-19 by PCR on nasal swab, with pneumonia with oxygen dependence (defined as the need for continuous oxygen supply to maintain pulse oximetry saturation, SpO₂ ≥93% or arterial gas with PaO₂ ≥60 mm Hg) and no previous hospitalisation within the last 6 months. Exclusion criteria were as follows: patients unable to give consent, were pregnant or breast feeding, required mechanical ventilation, were unable to maintain prolonged sitting position (≥2 hours) or had contraindications for HBO₂ therapy (such as acute respiratory distress syndrome (ARDS), emphysema, air cysts or bullae and untreated pneumothorax, or severe chronic obstructive pulmonary disease).

Treatment

All patients were treated following the latest guidelines of the National Ministry of Health of Argentina.¹⁶ Standard treatment for COVID-19 consisted of supportive treatment, regular

antimicrobial treatment for severe community-acquired pneumonia (ceftriaxone 2g/day and azithromycin 500mg/day for 7 days), dexamethasone 8mg/day, paracetamol 1 g/6 hours in case of high temperature and monitoring for complications. Oxygen was supplied with a reservoir mask.

Procedures

Participants were randomly assigned to receive either HBO₂ treatment in addition to the standard treatment (treatment group) or the standard treatment alone (control group) for respiratory symptoms. We used simple randomisation with number assignment by a random number generator (UX App) from 1 to 10 and entered into tables assigning odd or even number to treatment or control.

HBO₂ treatment consisted of ≥5 sessions of 90 min of hyperbaric oxygen therapy administered once daily using Revitalair technology (1.45 ATA) with an inspired fraction close to 100% of oxygen. As preventive measures, chambers were cleaned with a disinfectant with quaternary ammonium salts between patients and patients, and operators wore personal protection equipment when patients were transferred to the treatment room. The regimen of ≥5 sessions was chosen based on clinical experience with patients with hypoxaemia associated with COVID-19.¹⁰ However, if hypoxaemia was resolved with fewer sessions, that patient would not receive more sessions and would not be included in the study; this did not occur.

The choice of equipment with pressure at 1.45 ATA was based on multiple benefits: reduced possibility of lung injury, lower cost of the equipment (therefore higher possibility of meeting the demand), ease of installation (important in the context of the pandemic), the possibility of transporting the equipment and ease of operation and disinfection.^{12,13,15}

Prior to and after each treatment, SpO₂ evaluation was performed by removing the patient's oxygen mask and allowing them to breathe room air for ≥5 min while monitoring SpO₂ with a pulse oximeter finger probe. For patients in the control group, SpO₂ on room air was monitored three times per day, every 8 hours, and the morning measure was used in the study. A fractional inspired oxygen of 21% was used to define room air.

Outcomes

Primary outcomes were proportion of patients that recovered from hypoxaemia and at 3, 5 and 10 days (to assess if patient recovered after two and five sessions) and median time to recovery within 30 days. Normalisation of oxygen requirement (oxygen independence) was defined as pulse oximetry value in ambient air ≥93% and/or arterial blood gas with a partial pressure of oxygen (PaO₂) value of ≥60 mm Hg in ambient air. Secondary outcomes were the need for mechanical respiratory assistance, development of ARDS and mortality within 30 days. Adverse events related to HBO₂ therapy were recorded, including the presence of ear pain, ear obstruction, significant and constant changes in BP after 4 hours of treatment and HR, barotrauma or other symptoms.

Ethical considerations

All participants provided written informed consent, while all procedures were conducted in accordance with the principles of the World Medical Association Declaration of Helsinki. This study was carried out in compliance with Good Clinical Practice (GCP); personal data were protected and encrypted. Also, a programme of quality monitoring was performed during the clinical trial to adhere to GCP.

Patient and public involvement

No patient involved.

Statistics

Data were analysed with an intention-to-treat approach. Categorical variables were analysed with bivariate analysis using χ^2 test, or Fischer's test and described in percentages with 95% CIs. Continuous variables were analysed with Student's t-test and or paired t test, as appropriate and described using mean and SD or median with IQR, as appropriate, depending on distribution and analysis with Shapiro-Wilk test. Inferential analyses were performed using a bivariate analysis by calculating adjusted OR with 95% CIs and adjusted OR with a multiple logistic regression model. HRs were used for time to event. Log rank test and Cox regression were used to calculate HR, controlling for age, sex, arterial hypertension, obesity, diabetes, smoking and COPD. Statistical significance was set at $p < 0.05$. Statistical analyses were performed with Stata V.13.0.

Planned interim analysis

An interim analysis of the results was scheduled once 50% of the patients were recruited. An independent investigator presented a report of the analysis to the hospitals' ethics committee, and this authorised the early suspension of the study. Analysis was prespecified in the original protocol; outcomes were the proportion of recovery from hypoxaemia and at 3, 5 and 10 days and time to correct hypoxaemia. Following the methodology presented by Pocock,¹⁷ the p values for the interim analysis and the criteria to stop the trial based on clinical benefits were reported with adjusted error type I at 0.0294.

RESULTS

From July to November 2020, 40 patients were included. The study was stopped at interim analysis; analysis occurred after enrolment. The study was interrupted with the approval of each independent ethics committee when interim analysis with 50% of sample size showed a marked benefit of treatment. To that point, the cohort was as follows: 20 (50.0%) were assigned to HBO₂ treatment group and 20 (50.0%) to the control group. Of the 40 randomised, 39 completed the protocol (19 in HBO₂ group and 20 in the control group). One patient in the HBO₂ withdrew after the second session because of ear discomfort (figure 1).

Mean age was 55.2 ± 9.2 years, and 26 (65.0%) patients were male. Demographic and clinical characteristics are shown in table 1. Baseline demographics and clinical variables between the two groups were comparable (table 1). Baseline SpO₂ was $85.1\% \pm 4.3\%$ for the whole group, $86.5\% \pm 3.9\%$ in the treatment group and $84.1\% \pm 4.5\%$ in the control group, with no significant difference between the two groups ($p = 0.150$) (table 2).

Four (10.0%) of 40 patients had a poor clinical course (composite outcome of acute respiratory distress syndrome, mechanical ventilation requirements or death) within 30 days of admission, with 3 (15.0%) patients in the control group and 1 (5.0%) patient in the treatment group, with no statistically significant difference. Two (5.0%) patients died within 30 days after admission, one in each group. The use of HBO₂ treatment had no statistically significant effect on the incidence of ARDS, mechanical ventilation or death within 30 days after admission (table 2).

Patients included in the treatment group (n=20), including the patient who abandoned treatment, received an average of

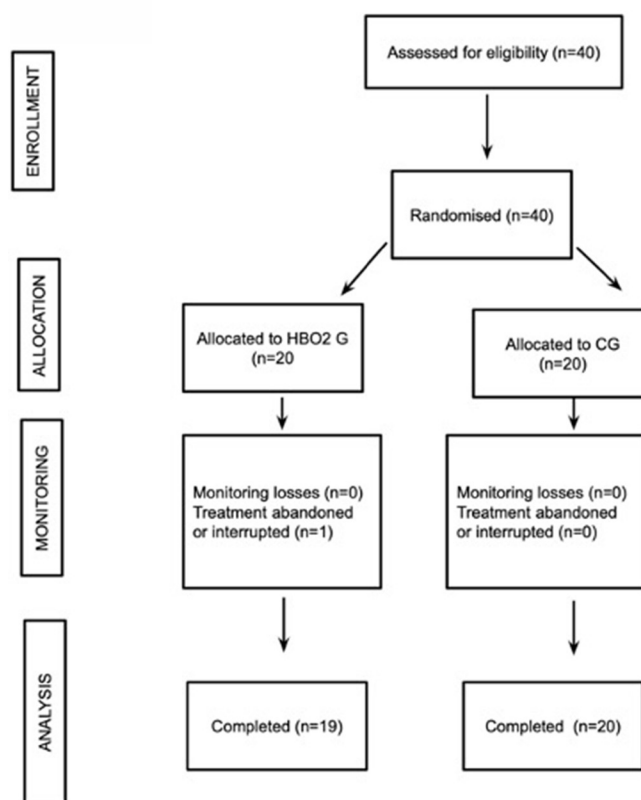


Figure 1 Flow chart of included patients. CG, control group; HBO₂, hyperbaric oxygen treatment group.

6.2 ± 1.2 hyperbaric oxygen sessions. The difference between arterial saturation at pre-HBO₂ and post-HBO₂ treatment session was significant for most sessions (table 3). SpO₂ showed an immediate and successive daily improvement at a higher slope compared with the patients who did not receive HBO₂ (table 3 and figure 2).

Hypoxaemia correction (defined as SpO₂ $\geq 93\%$) was reached in the HBO₂ treatment group, with a greater upward slope of arterial saturation compared with control group. Time to correct hypoxaemia was shorter in the treatment group compared with the control group: median (IQR) 3 (1.0–4.5) days versus 9 (5.5–12.5) days, respectively ($p < 0.010$), log rank χ^2 28.31, $p < 0.001$; HR 6.9 (95% CI 2.9 to 16.2); adjusted HR was 7.7 (95% CI 3.1 to 19.5) (z 4.3, $p < 0.001$). The OR of recovery from hypoxaemia in the HBO₂ group compared with the control group was 23.2 (95% CI 1.6 to 329.6; $p = 0.001$) at day 3 and 28.5 (95% CI 1.8 to 447.4; $p < 0.001$) at day 5 (table 2). Figure 3 shows computed tomography (CT) images of two patients at the beginning of HBO₂ treatment (figure 3A) and after receiving five sessions (figure 3B) and one patient in the control group at day 1 and 20 days later (figure 3C).

DISCUSSION

Our findings suggest that supplementing oxygen through HBO₂ treatment contributed to an increased SpO₂ in patients with COVID-19 with severe hypoxaemia, with no significant adverse effects. Cases of severe COVID-19 that need mechanical ventilation have a high mortality risk. Therefore, novel therapeutic strategies are needed, and this study offers evidence supporting HBO₂ treatment. Even in the context of the ED, a small number

Table 1 Demographic and clinical characteristics

Characteristic	Total, n=40	HBO ₂ , n=20	Control, n=20
Male, n (%)	26(65)	13(65)	13(65)
Age, years*	55.2±9.2	52.8±8.5	57.7±9.3
Weight, kg†	82.0 (90.0; 75.0)	79.5 (74.0; 90.0)	86.0 (79.0; 100.0)
Height, cm†	172.5 (169.5; 179.0)	171.0 (169.5; 174.0)	175.0 (170.5; 179.5)
BMI, kg/m ² †	27.7 (25.1; 30.3)	27.9 (24.7; 29.0)	27.2 (25.8; 32.1)
SAP, mm Hg†	120.0 (120.0; 130.0)	120.0 (115.0; 127.5)	125.0 (120.0;130.0)
DAP, mm Hg*	77.8±10.4	75.9±10.7	79.7±9.9
HR, bpm*	88.8±13.4	85.9±14.6	91.7±11.7
Respiratory rate, rpm*	26.4±4.6	25.3±0.9	27.4±1.0
Temperature, °C†	36.7 (36.4; 37.0)	36.8 (36.4; 37.2)	36.7 (36.4; 36.8)
Haematocrit %*	38.3±4.8	39±3.99	37.7±5.4
White cell count, /mm ³ *	9,008±3456	9,214±3209	8,803±3758
Lymphocytes, /mm ³ *	1,319±489	1,403±563	1,245±415
Platelets, ×1000/mm ³ †	281.5 (212.0; 352.5)	299.5 (268.1–372.0)	268.0 (105.5; 310.0)
Blood glucose, mg/dL†	109.0 (99.0; 119.5)	109.0 (101.5; 115.5)	107.0 (97.0; 199.5)
Urea, mg/dL†	39.0 (26.0; 46.0)	34.0 (24.0; 46.0)	40.5 (32.4; 45.5)
Creatinine, mg/dL†	0.88 (0.7; 1.1)	0.9 (0.7; 1.0)	0.9 (0.7; 1.1)
Sodium, mEq/L*	136.4±4.8	136.7±3.2	136.4±4.8
Potassium, mEq/L*	4.0±0.4	3.9±0.4	4.0±0.3
Comorbidity			
Obesity, n (%)	14 (35.0)	6 (30.0)	8 (40.0)
Hypertension, n (%)	13 (32.5)	8 (40.0)	5 (25.0)
Diabetes, n (%)	7 (17.5)	3 (15.0)	4 (20.0)
COPD, n (%)	2 (5.0)	0 (0.0)	2 (10.0)
Asthma, n (%)	2 (5.0)	2 (10.0)	0 (0.0)
CKD, n (%)	2 (5.0)	1 (5.0)	1 (5.0)
Cancer, n (%)	2 (5.0)	0 (0.0)	2 (10.0)
Symptoms, n (%)			
Fever	35 (87.5)	17 (85.0)	18 (90.0)
Odynophagia	17 (42.5)	10 (50.0)	7 (35.0)
Anosmia	6 (15.0)	4 (20.0)	2 (10.0)
Dysgeusia	7 (17.5)	4 (20.0)	3 (15.0)
Dyspnoea	37 (92.5)	19 (95.0)	18 (90.0)
Headache	4 (10.0)	2 (10.0)	2 (10.0)

Data are described as

*mean±SD.

†median (IQR).

BMI, body mass index; bpm, beats per minute; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DAP, diastolic arterial pressure; rpm, rate per minute; SAP, systolic arterial pressure.

of HBO₂ sessions, as shown in our findings, could benefit patients before they are transferred to intensive care.

Dyspnoea and hypoxaemia (SpO₂ <90% despite oxygen supplementation) have been added to a list of risk factors for mortality in patients with COVID-19 pneumonia, together with age, sex, comorbidities and inflammatory biomarkers.² In severe cases of COVID-19, there occurs an acute lung injury,

macrophage-neutrophil accumulation in the lungs and elevated proinflammatory serum cytokines.¹⁸ HBO₂ treatment involves the increasing partial pressure of oxygen in plasma and tissues, with improved diffusion efficiency of oxygen through the alveolar barrier, a higher content of dissolved oxygen in the blood and increased diffusion distance of oxygen.⁶ HBO₂ treatment may modulate the inflammatory response and the cytokine level,

Table 2 Outcomes within 30 days of diagnosis

Outcomes	Total (n=40)	HBO ₂ (n=20)	Control (n=20)	P value	Effect size (95% CI)
Days to normalisation*	5.0 (3.0; 9.0)	3.0 (1.0; 4.5)	9.0 (5.5; 12.5)	<0.010	HR 6.9 (2.9 to 16.2)
SpO ₂ ≥93% at 3 days, n (%)	12 (30)	11 (55)	1 (8)	0.001	OR 23.2 (1.6 to 329.6)
SpO ₂ ≥93% at 5 days, n (%)	27 (68)	19 (95)	8 (40)	<0.001	OR 28.5 (1.8 to 447.4)
SpO ₂ ≥93% at 10 days, n (%)	33 (83)	20 (100)	13(65)	0.004	∞
SpO ₂ ≥93% at 15 days, n (%)	36 (90)	20 (100)	16 (80)	0.106	∞
Acute respiratory distress, n (%)	4 (10)	1 (5)	3 (15)	0.605	OR 0.3 (0.0 to 3.4)
Mechanical ventilation, n (%)	4 (10)	1 (5)	3 (15)	0.605	OR 0.3 (0.0 to 3.4)
Death, n (%)	2 (5)	1 (5)	1 (5)	1.000	OR 1.0 (0.1 to 17.8)

* Median (25th percentile; 75th percentile).

SpO₂, oxygen saturation.

Table 3 Oxygen saturation response

Saturation assessment	Total (n=40)	HBO ₂ (n=20)	Control (n=20)	P value
SpO ₂ on day 1, %*	85.1±4.3	86.5±3.9	84.1±4.5	0.150
SpO ₂ on day 2, %*	86.7±4.6	89.0±4.1	84.4±3.9	<0.010‡
SpO ₂ on day 3, %*	87.9±3.1	89.6±2.8	86.4±2.5	<0.010‡
SpO ₂ on day 4, %†	89.0 (88.0; 92.0)	93.0 (91.0; 94.0)	88.0 (82.0; 89.0)	<0.010‡
SpO ₂ on day 5, %†	91.0 (88.0; 93.0)	93.0 (92.0; 95.0)	88.0 (87.0; 91.0)	<0.010‡
SpO ₂ on day 6, %†	93.0 (89.0; 94.0)	94.0 (93.5; 95.5)	90.0 (88.0; 92.0)	<0.010‡
SpO ₂ on day 7, %†	92.0 (90.0; 94.0)	94.0 (93.0; 95.0)	91.0 (89.5; 92.0)	0.020‡

Data are described as

*mean±SD.

†median (IQR).

‡Statistically significant.

SpO₂, oxygen saturation.

appearing to increase FGF production and collagen synthesis and decrease interleukin 1, interleukin 6 and tumour necrosis alpha factor; also, it has been suggested that the treatment may affect the expression levels of transforming growth factor beta-1 and platelet-derived growth factor.^{6 19–21} Moreover, COVID-19 related stressors exacerbate the effects of the disease by inducing the generation of oxidative stress, affecting the host's immune response and associated with systemic tissue damage.²² HBO₂ treatment below 2.0 ATA increases the activity of antioxidant enzymes, including first-line defence antioxidants superoxide dismutase and catalase.¹¹

Case series have reported that patients with COVID-19 treated with HBO₂ showed improved survival and could avoid mechanical ventilation.⁷ Our findings support case series suggesting the beneficial effect of HBO₂ in the correction of hypoxaemia. In case series, as suggested by Paganini *et al*,⁷ it is not possible to determine if improved outcomes were the effect of the treatment or time. Comparing our two groups, the effect of HBO₂ seems to be significantly more beneficial than receiving no treatment.

We acknowledge that this study has limitations. The interim analysis and early suspension because of clinical benefits (superiority and safety) should be taken into account; this limited conclusions about the secondary outcomes. Indeed, the small number of patients included in the study is an important limitation. Although not statistically significant, there is a trend towards younger patients in the treatment group. Also, data were acquired under emergency conditions; so, information on some variables could not be included, for example, baseline oxygen requirement. However, only patients with requirement

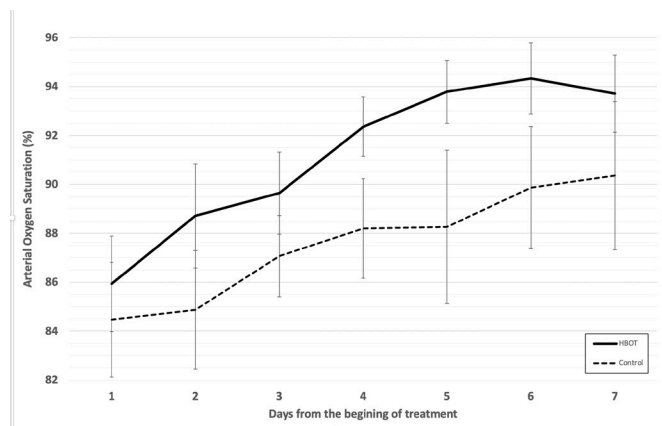


Figure 2 Improvement of arterial oxygen saturation over the course of treatment.

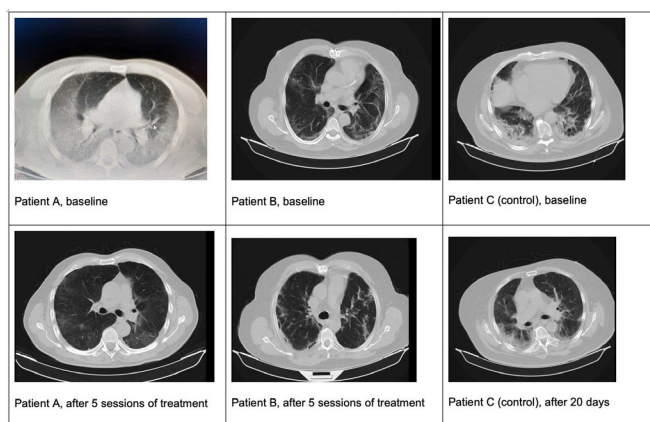


Figure 3 CT images of patients. Patients in treatment group (A and B) and patient in control group (C).

of high-flow oxygen were included. It was not possible to determine the moment hypoxaemia had been established, and HBO₂ could have been more effective in reducing mortality when hypoxaemia was recently established. Normalisation of oxygen was selected as the primary outcome because long-term hyperoxia induces more residual multisystemic inflammatory complications.² In fact, mortality depends on many other variables that could not be controlled in this study, such as previous days of hypoxaemia.

This treatment could be easily available in various settings. Portable hyperbaric chambers offer a fast setup to avoid transferring patients to other hospital areas, attenuating the risk of virus transmission. In conclusion, our findings support the efficacy of HBO₂ in the treatment of COVID-19 with severe hypoxaemia; larger trials are needed to further confirm the treatment effects on survival.

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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.

Patient consent for publication Consent obtained directly from patient(s)

Ethics approval Ethics committee of three participating hospitals: Municipal de San Isidro, Santojanni, Muñiz.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Additional information available on request to authors.

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