Hyperbaric oxygen therapy in preventing mechanical ventilation in COVID-19 patients: a retrospective case series

Objective: A pandemic afflicts the entire world. The highly contagious SARS-CoV-2 virus originated in Wuhan, China in late 2019 and rapidly spread across the entire globe. According to the World Health Organization (WHO), the novel Coronavirus (COVID-19)has infected more than two million people worldwide, causing over 160,000 deaths. Patients with COVID-19 disease present with a wide array of symptoms, ranging from mild flu-like complaints to life threatening pulmonary and cardiac complications. Older people and patients with underlying disease have an increased risk of developing severe acute respiratory syndrome (SARS) requiring mechanical ventilation. Once intubated, mortality increases exponentially. A number of pharmacologic regimens, including hydroxychloroquine-azithromycin, antiviral therapy (eg, remdesevir), and anti-IL-6 agents (e.g., toclizumab), have been highlighted by investigators over the course of the pandemic, based on the therapy's potential to interrupt the viral life-cycle of SARS-CoV-2 or preventing cytokine storm. At present, there have been no conclusive series of reproducible randomised clinical trials demonstrating the efficacy of any one drug or therapy for COVID-19.

Cases: COVID-19 positive patients (n=5) at a single institution received hyperbaric oxygen therapy (HBOT) between 13 and 20 April 2020. All the patients had tachypnoea and low oxygen saturation despite receiving high FiO_2. HBOT was added to prevent the need for mechanical ventilation. A standard dive profile of 2.0ATA for 90 minutes was employed. Patients received between one and six treatments in one of two dedicated monoplace hyperbaric chambers.

Results: All the patients recovered without the need for mechanical ventilation. Following HBOT, oxygen saturation increased, tachypnoea resolved and inflammatory markers fell. At the time of writing, three of the five patients have been discharged from the hospital and two remain in stable condition.

Conclusion: This small sample of patients exhibited dramatic improvement with HBOT. Most importantly, HBOT potentially prevented the need for mechanical ventilation. Larger studies are likely to define the role of HBOT in the treatment of this novel disease.

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COVID-19 • HBOT • oxygen saturation • SARS • SARS-CoV-2 • ventilation

The highly contagious SARS-CoV-2 virus, thought to have originated in Wuhan, China, has infected more than two million people at the time of writing.[1] In the US alone, the death toll exceeds 40,000 people.[2] The pathogenic SARS-CoV-2, a single-stranded, RNA-enveloped virus, causes respiratory disease in humans.[3] The clinical presentation varies from asymptomatic SARS-CoV-2 positive patients to life threatening cardiac and pulmonary complications. An article in the *Journal of the American Medican Association* (*JAMA*) in February 2020 from Wuhan, China reported that 26% of infected patients required intensive care with a mortality rate of 4.3%.[4] Older people and patients with multiple comorbidities have an increased risk of severe acute respiratory syndrome (SARS) and death. In addition, an elevated D-dimer (a product of fibrinogen degradation that indicates a prothrombotic state) on admission corresponds with a poor outcome.[5,6] Finally, once the patient requires mechanical ventilation, the risk of mortality rises sharply.[7]

In the absence of effective therapy, social distancing has helped to decrease the rate of those in the general population becoming infected in an attempt to avoid overwhelming the existing healthcare infrastructures. For patients who contract the virus and develop serious respiratory disease, the solution must entail successful treatment options. At the time of this writing, there are no US Food and Drug Administration (FDA) approved medications or therapies for COVID-19. A search of clinicaltrials.gov reveals over 300 clinical trials ongoing or preparing to enrol for COVID-19 disease.[8] These trials focus primarily on pharmacologic therapies based on interrupting the viral life-cycle or preventing cytokine storm and include hydroxychloroquine- azithromycin, antiviral therapy (for example, remdesevir), and anti-IL-6 agents (for example, toclizumab).[9]

Hyperbaric oxygen treatment (HBOT) is an FDA-approved medical treatment with several indications including wound healing, late effects of radiation therapy, necrotising fasciitis, compromised flaps, carbon monoxide poisoning and air diving decompression illness.[10] In the hyperbaric chamber, the patient

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Table 1. Baseline patient characteristics (n=5)

Age, years	
Median	48
Interquartile range	39–63
Gender	
Female	4 (80%)
Male	1 (20%)
Ethnicity	
African American	3 (60%)
Hispanic or Latino	0 (0%)
White	2 (40%)
Comorbidities	
Obesity	4 (80%)
Diabetes	3 (60%)
Hypertension	4 (80%)
Viral pneumonia	2 (40%)

breathes 100% oxygen at 1–1.5 times atmospheric pressure. The increased pressure results in increased dissolved oxygen in the plasma and tissues. Theoretically, HBOT could address the hallmarks of severe COVID-19 disease: progressive hypoxia and pulmonary inflammation. The exact mechanism of action is unclear. However, ultra-high oxygen levels may have several antiviral effects: increasing the production of viricidal free oxygen radicals,[11] upregulating hypoxic inducible factor (HIF), which in turn stimulates the production of antiviral peptides such as defensins and cathelicidins, and reducing proinflammatory cytokines such as IL-6 responsible for cytokine storm.[12]

The first reported use of HBOT in COVID-19 disease came from Wuhan, China. There were five patients who received HBOT for severe respiratory disease: two described as having critical disease and three with severe disease. The primary criteria for HBOT was impending intubation, i.e., increased oxygen requirements wiht falling sauration and severe tachypnoea. The rapid resolution of tachypnoea and correction of hypoxia was observed in all five patients. No complications related to the HBOT were reported.[13]

Table 2. Oxygen saturation and respiratory rate pre-and post-hyperbaric oxygen therapy (HBOT)

	Pre-HBOT Mean±SD	Post-HBOT Mean±SD	At 24 hours* Mean±SD
Oxygen saturation, %	95.5±2.61	94.6±2.30	96±1.41
Respiratory rate, breaths/minute	35.4±8.47	28±7.55	—

SD-standard deviation; *after HBOT treatment

As the disease spread to the US, physicians considered using HBOT as part of the treatment regimen for COVID-19 disease. There are no contraindications to the use of HBOT in patients with viral pneumonia or SARS. The only absolute contraindication to HBOT is an untreated pneumothorax.[14]

Methods

On 13 April 2020, the pulmonologist at Opelousas General Health System consulted the hyperbaric team for a 48-year-old African American woman complaining of severe shortness of breath with a respiratory rate nearing 50 breaths/minute. Her oxygen saturation was falling despite having received highflow humidified oxygen (Vapotherm Inc., US). Her comorbidities included hypertension, obesity and sleep apnoea. This was her fifth day in the intensive care unit. Her D-dimer reached a peak of 12,070mg/ml. The pulmonologist planned to intubate the patient within the hour. After obtaining informed consent for the compassionate use of HBOT, she underwent 90 minutes of HBOT at 2.0ATA. Her shortness of breath immediately improved, her oxygen saturation stabilised, and her D-dimer fell to 4,324mg/ml in less than 24 hours. The pulmonologist decided against mechanical ventilation. For the next five days, the patient received daily HBOT resulting in complete resolution of her tachypnoea. Currently, the patient is resting comfortably with an oxygen (O_2) saturation of 97% on 45% FiO_2.

Between 13 and 20 April, the hyperbaric team treated another four COVID-19 patients with symptomatic respiratory disease and increasing oxygen requirements, and each of whom were facing impending intubation. The pulmonologist consulted the hyperbaric unit when mechanical ventilation was indicated as the next step in the patients' management, and the clinical decision was made to implement HBOT. All patients consented to the off-label use of HBOT before receiving therapy. Patient demographics are summarised in Table 1. There were four females and one male treated; three patients were African American and two patients were white.

Results

Reducing the need for mechanical ventilation was the primary objective for the compassionate use of HBOT in these patients (n=5). Fortunately, none of the patients treated with symptomatic COVID-19 disease needed a ventilator. In addition, all the patients had rapid resolution of their tachypnoea and improved oxygen saturation (Table 2, Fig 1 and 2). Similarly, laboratory values trended toward improvement post-HBOT, although there was not enough data to draw any conclusions. The number of hyperbaric treatments required per patient ranged from one to six, with an average of five. Less than a week following their last HBOT treatment, three patients were discharged and two remain hospitalised in a stable condition. There were no complications related to treatment with HBOT.

Discussion

Encountering a previously unknown contagion, challenges health professionals to find effective therapies in a timely fashion. The current treatment of COVID-19 disease is limited to supportive care. However, in older people and patients with underlying disease, traditional supportive care often fails, necessitating mechanical ventilation. Once on the ventilator, COVID-19 patients are difficult to wean and the risk of mortality rises sharply. The search for an efficacious treatment continues in earnest. As a start, investigating drugs and devices that are already FDA-approved and have well-established safety profiles will hasten the discovery and timely implementation of lifesaving therapies. HBOT has decades of proven safety data in patients with multiple comorbidities.[15] In addition, the hyperoxygenation created by breathing oxygen under pressure may reverse the hypoxia caused by the SARS-CoV-2 virus. Combined with its anti-inflammatory and potential viricidal properties, HBOT is an attractive candidate for study in the treatment of COVID-19 disease.

In this small case series of patients with moderately severe COVID-19 disease, the multispecialty physicians at Opelousas General Health System achieved their primary goal of avoiding mechanical ventilation. Patients reported the prompt resolution of laboured breathing following a single HBOT treatment. As expected, the rise in oxygen saturation values accompanied the improved symptoms. A decrease in oxygen requirement below an FiO_2 of 50% took between one and six HBOT sessions, with an average of five HBOT treatments per patient. The results are similar to the case series from Wuhan, China.[5]

The compassionate use of HBOT was used in patients that could not wait for an approved protocol. Subsequent to this, a protocol for the use of HBOT in patients with COVID-19 has been drafted and is available online.[16] In addition, we have created an app for use by physicians to submit information on patients with COVID-19 and treated with HBOT that will be held on a registry which would be used, once approved, as part of a further study on this issue.

Limitations

The sample size in this case series underscores the primary limitation of the study: five patients is a small number and extrapolating the data to the population in general will require prospective clinical trials with greater power. In addition, the predominance of female patients with serious disease (i.e., COVID-19) is not consistent with previous reports[17] but it should also be noted that the greater risk of respiratory failure among African Americans has been reported by the Centers for Disease Control and Prevention.[18]

Fig 1. Oxygen saturation. HBOT—hyperbaric oxygen therapy

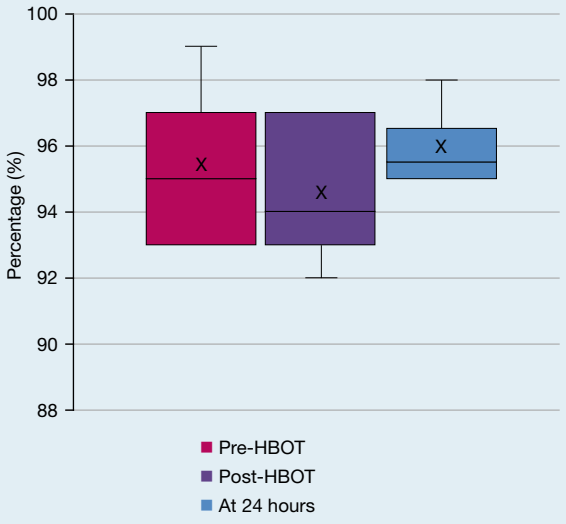
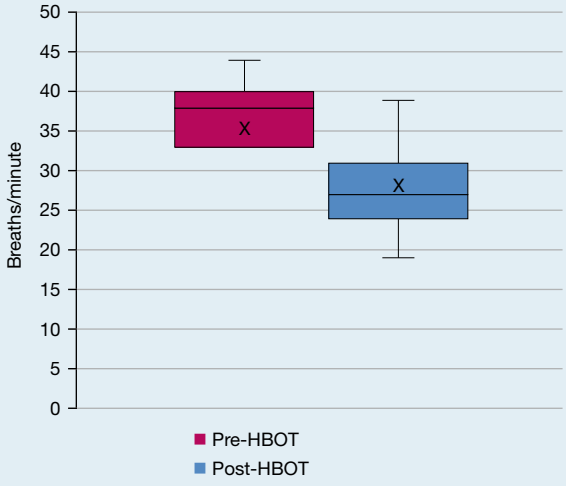


Fig 2. Respiratory rate. HBOT—hyperbaric oxygen therapy



Conclusion

In conclusion, this study supports further research into the efficacy of HBOT in the treatment of symptomatic COVID-19 disease. The authors continue to offer HBOT for compassionate use; however, a larger prospective clinical trial is needed to clearly define the role of HBOT in this population. **JWC**

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