RESEARCH ARTICLE

Hyperbaric oxygen therapy for COVID-19 patients with respiratory distress: treated cases versus propensity-matched controls

Scott A. Gorenstein, MD [1,2]; Michael L. Castellano, MD [1,2]; Eric S. Slone, MD [1,2]; Brian Gillette, PhD [1,2]; Helen Liu, DO [1,2]; Cindy Alsamarraie [1,2]; Alan M. Jacobson, MD [2,3]; Stephen P. Wall, MD [4,5]; Samrachana Adhikari, PhD [5]; Jordan L. Swartz, MD [4]; Jenica J.S. McMullen, MD [4]; Marcela Osorio [4]; Christian A. Koziatek, MD [4]; David C. Lee, MD [4,5]

[1] Division of Wound Care, Department of Surgery, NYU Winthrop Hospital, New York, NY, U.S.

[2] NYU Long Island School of Medicine, New York, NY, U.S.

[3] Foundations of Medicine Department, NYU Winthrop Hospital, New York, NY, U.S.

[4] Department of Emergency Medicine, NYU Grossman School of Medicine, New York, NY, U.S.

[5] Department of Population Health, NYU Grossman School of Medicine, New York, NY, U.S.

CORRESPONDING AUTHORS: Scott A. Gorenstein – *scott.gorenstein@nyulangone.org*
David C. Lee – *david.lee@nyumc.org*

ABSTRACT

Objective: Given the high mortality and prolonged duration of mechanical ventilation of COVID-19 patients, we evaluated the safety and efficacy of hyperbaric oxygen for COVID-19 patients with respiratory distress.

Methods: This is a single-center clinical trial of COVID-19 patients at NYU Winthrop Hospital from March 31 to April 28, 2020. Patients in this trial received hyperbaric oxygen therapy at 2.0 atmospheres of pressure in monoplace hyperbaric chambers for 90 minutes daily for a maximum of five total treatments. Controls were identified using propensity score matching among COVID-19 patients admitted during the same time period. Using competing-risks survival regression, we analyzed our primary outcome of inpatient mortality and secondary outcome of mechanical ventilation.

Results: We treated 20 COVID-19 patients with hyperbaric oxygen. Ages ranged from 30 to 79 years with an oxygen requirement ranging from 2 to 15 liters on hospital days 0 to 14. Of these 20 patients, two (10%) were intubated and died, and none remain hospitalized. Among 60 propensity-matched controls based on age, sex, body mass index, coronary artery disease, troponin, D-dimer, hospital day, and oxygen requirement, 18 (30%) were intubated, 13 (22%) have died, and three (5%) remain hospitalized (with one still requiring mechanical ventilation). Assuming no further deaths among controls, we estimate that the adjusted subdistribution hazard ratios were 0.37 for inpatient mortality (p=0.14) and 0.26 for mechanical ventilation (p=0.046).

Conclusions: Though limited by its study design, our results demonstrate the safety of hyperbaric oxygen among COVID-19 patients and strongly suggests the need for a well-designed, multi-center randomized control trial. ∎

INTRODUCTION

The respiratory distress caused by the novel coronavirus 2019 (COVID-19) is characterized by severe hypoxia thought to be induced by a cytokine storm [1-3]. The hypoxia due to COVID-19 can be profound, and some patients have a severe oxygen debt without significant hypercapnia or signs of respiratory distress [4]. Unfortunately, the treatment options for novel viruses like severe acute respiratory syndrome (SARS), middle east respiratory syndrome (MERS), and now COVID-19 have been limited [5,6].

Currently, hyperbaric oxygen (HBO_2) therapy is an FDA-approved therapy for specific conditions (e.g., carbon monoxide poisoning and certain non-healing wounds) [7,8]. Based on physiology, HBO_2 therapy may reverse the severe hypoxia of COVID-19 by increasing the partial pressure of oxygen at higher atmospheric pressures [9,10]. Several studies in cellular models and patients with conditions like avascular necrosis have also demonstrated an inhibitory effect of HBO_2 therapy on proinflammatory cytokine production, with measurable decreases in markers such as interleukin-6 [11-14]. However, the increased pressures of HBO_2 therapy may increase acute lung injury or induce pulmonary edema among COVID-19 patients, so its safety must be evaluated [15-17].

Two reports of COVID-19 patients in Wuhan, China, and in Louisiana have suggested that HBO_2 therapy may

KEYWORDS: COVID-19; hyperbaric oxygen therapy; infectious diseases

lead to faster clinical improvement when compared to patients on other treatments such as extracorporeal membrane oxygenation (ECMO) or mechanical ventilation [18-20]. To our knowledge there has not been a formal study of HBO_2 therapy among COVID-19 patients using comparison to controls of any kind. The purpose of this clinical trial was to perform an initial analysis of the safety of HBO_2 therapy among COVID-19 patients and provide some preliminary evidence on its possible efficacy. It also highlights important considerations that must be addressed before any providers consider HBO_2 therapy for COVID-19 patients.

METHODS

Study design and setting

This was a clinical trial of HBO_2 therapy among COVID-19 patients admitted between March 31 and April 28, 2020. All patients treated with HBO_2 therapy were consented and enrolled at NYU Winthrop Hospital. Propensity-matched controls were obtained using data among COVID-19 patients admitted at NYU Winthrop Hospital over the same time period. This study was approved by the Institutional Review Board (IRB) at NYU Langone Health.

Prior to commencing the study we contacted the Food and Drug Administration (FDA), who stated that the non-significant risk assessment made by our IRB was sufficient to determine that an investigational device exemption (IDE) was not required to start the study. This study's registration number at *clinicaltrials.gov* is NCT04332081. Our target enrollment was 40 cases in total. Here we report the results of the first 20 patients treated in this planned interim analysis.

Participants

Patients aged 18 years or older with a laboratory-confirmed diagnosis of COVID-19 were eligible for enrollment. Patients had to have an oxygen saturation lower than 93% on room air, understand the theoretical risks and benefits of participating, and have signed informed consent. Patients were excluded if they were pregnant or had a pneumothorax. An important exclusion that was added to the original protocol were patients with a positive troponin (see Discussion).

Participants were recruited into the trial from among inpatient admissions upon request by the hospitalist service. A physician certified in hyperbaric therapy provided a consultation to evaluate patients for eligibility and consent participants. Enrollment in other clinical trials was not an exclusion criterion. A total of 26 patients were evaluated, and six were excluded. Two were excluded for relative contraindications (e.g., ongoing seizures, as seizures can be provoked by HBO_2; and cardiac dysrhythmia, given that our protocol at the time did not include cardiac monitoring). Three were excluded as they were ineligible (e.g., lack of an oxygen requirement, positive troponin, and acute intoxication preventing consent). One patient was consented the day before, but became critically ill, required dialysis and was shortly intubated (See Appendix for flow diagram).

Intervention

Patients received 90 minutes of HBO_2 therapy at 2.0 atmospheres without air breaks. Patients received up to five treatments administered daily in addition to standard care, as long as they continued to require supplemental oxygen. Treatments were administered using Perry/Baromed chambers staffed with certified hyperbaric technicians. All treatments were supervised by a physician with hyperbaric medicine privileges at NYU Winthrop Hospital with ACLS certification and advanced airway management equipment.

Propensity-matched controls

Our prespecified plan was to identify controls among COVID-19 patients treated at NYU Winthrop Hospital using propensity score matching with a 3:1 ratio. Propensity scores were calculated using a multivariable logistic regression model to predict the likelihood of receiving HBO_2 therapy. We planned to use age, sex, comorbidities (e.g., coronary artery disease), and laboratory markers (e.g., D-dimer) to match controls to cases based on known risk factors for poor outcomes among COVID-19 patients [18]. However, given that patients were enrolled in the study on different hospital days (since admission) and each had different oxygen requirements, we added these variables to our matching criteria. Positive troponin and high body mass index (BMI) have been subsequently identified as additional risk factors and were added to the matching criteria [21,22]. Because approaches to care were rapidly evolving and new treatments were being employed through clinical trials during the course of the study, matched controls were selected from the same time period when cases were admitted to the hospital.

Primary and secondary outcomes

Our primary outcome was inpatient mortality; secondary outcomes were the need for mechanical ventilation and days on mechanical ventilation, which were all prespecified in our original protocol. Since some study patients were still intubated at the time of this report, we did not analyze days on mechanical ventilation.

Data sources

Electronic health records for COVID-19 positive admissions were queried from the Epic Systems Clarity database using Oracle SQL Developer on April 29, 2020. The exported data included demographic variables (i.e., age, sex, race/ethnicity), clinical variables (i.e., medical comorbidities based on past medical history and problem lists, BMI, laboratory values, oxygen flow and device), and clinical outcome data (i.e., date/time of arrival, death, intubation, or discharge).

To identify potential controls, we built a database of other hospitalized COVID-19 patients with their most recent laboratory values along with their daily maximum and median oxygen requirements in liters per minute for each 24-hour period since the arrival time for each patient.

These potential controls were then matched to cases by using propensity scores based on the predetermined criteria described above on a 3:1 ratio without replacement. On May 5, 2020, controls were selected by a statistician who was blinded to the patient outcomes. Then two physicians from the study team reviewed all cases and controls from May 6 to 22, 2020; they analyzed whether patients had been intubated or had died and recorded the hospital day when these events had occurred. They also determined if any patients had received any other experimental medications or were enrolled in other clinical trials for COVID-19.

Statistical analysis

Prior to any analysis of outcomes among controls we predetermined that we would exclude patients with a history of chronic obstructive pulmonary disease, cancer, cirrhosis, chronic kidney disease, or immunosuppression given that none of our HBO_2 therapy-treated cases had a history of these conditions. We also excluded any patients above the age of 80, BMI greater than 45, hospital day of 16 or longer, or oxygen requirement of 16 liters or more on what would have been equivalent to the day before or the day of HBO_2 therapy treatment, as none of our HBO_2 therapy-treated patients met these criteria.

After these exclusions we had 363 admitted COVID-19 patients to select as possible controls. Propensity score matching was performed using the nearest neighbor matching strategy to calculate the proximity of matches to cases. To evaluate the quality of matching, standardized mean differences (the most common statistic used to examine the balance of covariates between cases and propensity-matched controls) were analyzed to determine if any values were greater than 0.1 and performed an adjusted analysis by including these variables in our competing risks regression [23].

We first described our cases and controls based on demographic, clinical variables, and treatment with other medications for COVID-19 using summary statistics (i.e., Fisher's exact tests, t-tests, and rank-sum analyses, as appropriate). Since some study patients were still hospitalized, we used competing risks regression survival analysis to assess our primary outcome of time to inpatient mortality since treatment and secondary outcome of time to mechanical ventilation [24]. Competing outcomes for death included hospital discharge, and competing outcomes for mechanical ventilation included death prior to intubation (e.g., do-not-resuscitate status or medical futility) or hospital discharge. All statistical analyses were performed either in R 6.1 or Stata 16.1.

RESULTS

Study population

Among the first 20 cases treated with HBO_2 therapy, ages ranged from 30 to 79; patients were predominately male (90%); BMI ranged from 19 to 42; 10% had a history of coronary artery disease; hospital day before HBO_2 therapy ranged from 0 to 14 days; and baseline oxygen requirement ranged from 2 to 15 liters. Among our propensity-matched controls, the standardized mean differences for matched variables were less than 0.1 except for age (0.19), D-dimer (0.29), and baseline oxygen requirement (0.23). On average, controls were slightly older and had higher D-dimer values compared to cases. However, baseline oxygen requirements were higher among cases when compared to controls. Controls did not demonstrate any significant differences in characteristics that were not matched including history of hypertension, hyperlipidemia, diabetes, asthma, nor baseline ferritin, C-reactive protein or lactate dehydrogenase, nor in frequency of treatment or enrollment in clinical trials with other COVID-19 therapies (Table 1).

Table 1: Characteristics of COVID-19 patients treated with hyperbaric oxygen therapy and propensity-matched controls

patient characteristics	treated cases (n=20)	matched controls (n=60)	significance for difference
age			
average	58.4	60.9	0.41
median	58	62	0.42
range	30 to 79	24 to 80	
sex			
male	18 (90%)	55 (92%)	1.00
race			
White	7 (35%)	16 (27%)	0.90
Black	3 (15%)	10 (17%)	
Asian	1 (5%)	6 (10%)	
other	9 (45%)	28 (46%)	
body mass index			
average	29.7	29.0	0.63
median	28.0	28.5	0.72
range	19 to 42	23 to 44	
comorbidities			
hypertension	10 (50%)	24 (40%)	0.45
hyperlipidemia	6 (30%)	27 (45%)	0.30
diabetes	6 (30%)	22 (37%)	0.79
asthma	1 (5%)	2 (3%)	1.00
coronary artery disease	2 (10%)	7 (12%)	1.00
hospital day before treatment*			
average	3.0	2.8	0.83
median	2	1	0.71
range	0 to 14	0 to 14	
day 0 to 1	10 (50%)	33 (55%)	
day 2 to 4	5 (25%)	14 (23%)	
day 5 to 14	5 (25%)	13 (22%)	
baseline oxygen requirement			
average	8.6	7.4	0.43
median	6.5	5.0	0.16
range	2 to 15	1 to 15	
1 to 5 liters	7 (35%)	32 (53%)	
6 to 11 liters	6 (30%)	8 (14%)	
12 to 15 liters	7 (35%)	20 (33%)	
baseline laboratory values			
troponin			
negative	20 (100%)	60 (100%)	N/A
D-dimer			
average	1142	1870	0.61
median	375	389	0.66
ferritin			
average	1490	1382	0.71
median	1265	1151	0.46
C-reactive protein			
average	120	137	0.45
median	108	125	0.56
lactate dehydrogenase			
average	496	475	0.70
median	460	436	0.43
other COVID-19 treatments/trials			
azithromycin	16 (80%)	53 (88%)	0.45
hydroxychloroquine	18 (90%)	59 (98%)	0.15
anti-IL6 immuno-modulator	12 (60%)	26 (43%)	0.21
convalescent plasma	4 (20%)	6 (10%)	0.26
remdesivir	0 (0%)	1 (2%)	1.00

Notes: Propensity-matched controls by age, sex, history of coronary artery disease, BMI, hospital day before treatment, troponin, D-dimer. Exclude patients with a history of chronic obstructive pulmonary disease, cancer, cirrhosis, or chronic kidney disease.
* For controls, hospital day before treatment represents the matched day before when the patient would have had HBO_2 therapy.

Patient outcomes

Among the first 20 cases treated with HBO_2 therapy a total of 18 (90%) have been discharged (none required mechanical ventilation), two (10%) required mechanical ventilation and subsequently died. Among the 60 propensity-matched controls 44 (73%) have been discharged (with five requiring mechanical ventilation), three (5%) are still hospitalized (two required mechanical ventilation, and one still on mechanical ventilation), and 13 (22%) have died at the time of this interim analysis. We stratified these patient outcomes by baseline oxygen requirement in Table 2.

Table 2: Comparisons of outcomes of COVID-19 patients treated with hyperbaric oxygen therapy and propensity-matched controls

patient outcomes	treated cases (n=20)	matched controls (n=60)
all patients		
discharged		
never mechanically ventilated	18 (90%)	39 (65%)
required mechanical ventilation	0 (0%)	5 (8%)
still hospitalized		
never mechanically ventilated	0 (0%)	1 (2%)
required mechanical ventilation	0 (0%)	2 (3%)
inpatient death		
was not mechanically ventilated	0 (0%)	2 (3%)
required mechanical ventilation	2 (10%)	11 (18%)
baseline oxygen requirement 1 to 5 Liters		
discharged		
never mechanically ventilated	7 (100%)	31 (97%)
required mechanical ventilation	0 (0%)	0 (0%)
still hospitalized		
never mechanically ventilated	0 (0%)	0 (0%)
required mechanical ventilation	0 (0%)	0 (0%)
inpatient death		
was not mechanically ventilated	0 (0%)	0 (0%)
required mechanical ventilation	0 (0%)	1 (3%)
baseline oxygen requirement 6 to 11 Liters		
discharged		
never mechanically ventilated	6 (100%)	3 (38%)
required mechanical ventilation	0 (0%)	1 (12%)
still hospitalized		
never mechanically ventilated	0 (0%)	0 (0%)
required mechanical ventilation	0 (0%)	0 (0%)
inpatient death		
was not mechanically ventilated	0 (0%)	0 (0%)
required mechanical ventilation	0 (0%)	4 (50%)
baseline oxygen requirement 12 to 15 Liters		
discharged		
never mechanically ventilated	5 (71%)	5 (25%)
required mechanical ventilation	0 (0%)	4 (20%)
still hospitalized		
never mechanically ventilated	0 (0%)	1 (5%)
required mechanical ventilation	0 (0%)	2 (10%)
inpatient death		
was not mechanically ventilated	0 (0%)	2 (10%)
required mechanical ventilation	2 (29%)	6 (30%)

Note: Baseline oxygen requirement refers to the median oxygen flow on the day prior to treatment with HBO_2 therapy or for controls the day prior to when the patient would have received HBO_2 therapy, which was used as one of the matching criteria.

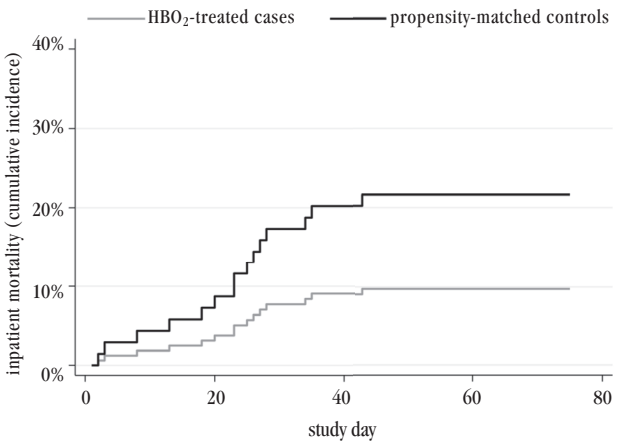
Safety profile of HBO_2 therapy

The few adverse events experienced among patients included epistaxis (which was not related to HBO_2 therapy treatment), ear pain, and claustrophobia. These events were deemed minor, but some patients were discontinued from further therapy (the patient with epistaxis was on full-dose anticoagulation and theoretically may have not been able to equalize ear pressures during HBO_2 therapy). There was one serious adverse event that resulted in a hold of the study, which is pending FDA review. In this case, the patient had arrived for his second treatment with an oxygen saturation of 66%. This improved to 88% during transfer after the 90-minute session. Shortly after his return to the inpatient ward, he was found on the floor between his bed and the bathroom. He was off his supplemental oxygen and had sustained a hypoxic arrest. He was intubated and resuscitated, but ultimately died after a prolonged hospitalization. Though it was internally concluded that the event was not directly related to the HBO_2 therapy itself, it demonstrates the high risk of transferring and caring for COVID-19 patients.

Competing risks survival analysis

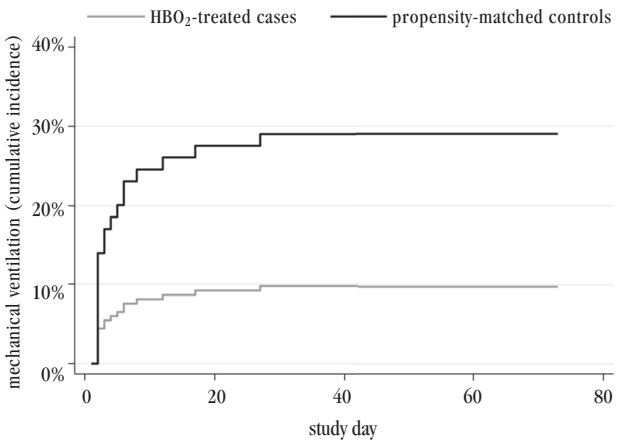
For our survival analysis we conservatively assumed that there would be no additional deaths or intubations among the three controls who are still hospitalized. We calculated that the unadjusted subdistribution hazard ratio for time to death was 0.42 (p-value = 0.24, 95% CI of 0.10 to 1.79) when comparing cases treated with HBO_2 therapy to propensity-matched controls. After adjusting for variables with a standardized mean difference greater than 0.1, the adjusted subdistribution hazard ratio for inpatient mortality was 0.37 (p-value = 0.14, 95% CI of 0.10 to 1.37).

Figure 1



Cumulative incidence curves for inpatient mortality among COVID-19 patients treated with hyperbaric oxygen therapy versus propensity-matched controls

Figure 2



Cumulative incidence curves for mechanical ventilation among COVID-19 patients treated with hyperbaric oxygen therapy versus propensity-matched controls

For time to mechanical ventilation we calculated that the unadjusted subdistribution hazard ratio was 0.30 (p-value = 0.09, 95% CI of 0.07 to 1.23) when comparing cases treated with HBO_2 therapy to propensity-matched controls. After adjusting for variables with a standardized mean difference greater than 0.1, the adjusted subdistribution hazard ratio was 0.26 (p-value = 0.046, 95% CI of 0.07 to 0.98). Cumulative incidence curves for these outcomes are depicted in Figures 1 and 2.

Limitations

Our study was performed at a single site, and patients were not randomized. Recruitment required a consult to be placed by the inpatient team and evaluation by a hyperbaric physician, which are potential sources of selection bias. Controls may have had relative contraindications to hyperbaric oxygen therapy that could not be assessed without a consultation by a hyperbaric specialist. We also excluded patients with a positive troponin level, and cases did not have certain medical comorbidities, which limits the generalizability of our results. Our study population was predominately male, which may limit the generalizability of our results to female patients. Furthermore, exclusion of these comorbidities and patient matching was based on electronic health records, which may not always be accurate. Matching variables were chosen based on known COVID-19 risk factors; however, accurate prognostic models for COVID-19 have not yet been established [25]. The small sample size in the study may limit the precision of our propensity score matching. Given a mortality rate of 25% among hospitalized COVID-19 patients, our sample size of 40 cases and 120 matched controls would have 80% power at an alpha of 0.05 to identify a 16.6% absolute reduction in mortality or a risk reduction ratio of 0.34. However, given this planned interim analysis, the sample size should have been adjusted to reduce the likelihood of a type I error. Finally, we found no significant differences between the characteristics of cases and controls, but this finding may be an artifact of our low sample sizes.

DISCUSSION

At the time of this presentation there have already been more than 600,000 deaths due to COVID-19 worldwide, and these numbers are expected to grow [26-28]. HBO_2 therapy has a direct effect on increasing oxygenation, can reduce inflammation, and has been used safely for decades with few complications [29-31]. However, HBO_2 therapy has received little focus as a therapeutic option for COVID-19 patients. Our study represents the largest known sample of patients treated with hyperbaric oxygen, and we report our preliminary findings.

In this interim analysis we find early evidence that suggests that HBO_2 therapy could be effective among COVID-19 patients while being safe in this population. These findings should be taken with caution given the few patients treated in our study. Furthermore, though every effort was made to identify matched controls to the cases treated with HBO_2 therapy, it is possible that there are unobserved differences between the cases and controls in our study that account for any differences in mortality or rates of mechanical ventilation [32]. In addition, the results in our survival analysis for inpatient mortality were not statistically significant, and the results for mechanical ventilation may have been due to chance. Therefore, this study cannot be taken as evidence of efficacy, but does highlight the need for a larger, multicenter, randomized control trial to be performed, as we know that there has been significant difficulty gaining traction for these studies to occur.

Based on the severe adverse event that occurred, a process improvement plan was enacted so that the receiving team would be made aware of the patient condition prior to leaving the hyperbaric unit; now patients are closely monitored for hypoxia via direct observation for at least one hour on pulse oximetry after being returned to the ward. This improvement in the transitions of care was put into place for all COVID-19 patients being transported to other areas of the hospital, as it is clear that the transport of these patients is a high-risk event. Our preliminary findings may spur some patients or providers to consider the treatment of COVID-19 patients in outpatient HBO_2 therapy centers that exist across the country. However, our experience has shown that these patients are very high-risk and need to be closely followed in a monitored setting.

Furthermore, our study had several exclusion criteria, and the first 20 patients had certain important characteristics. Notably, none of our patients had a positive troponin level, which was added as an exclusion because we had some concerns that impaired cardiac function may lead to hypotension or pulmonary edema. However, we are not suggesting that a positive troponin should be an absolute contraindication of HBO_2 among COVID-19 patients. In this initial study we added this exclusion to err on the side of caution. In addition, most of our patients were free of many significant medical comorbidities such as chronic obstructive pulmonary disease, cancer, cirrhosis, or chronic kidney disease, any of which may increase the likelihood of poor outcomes among COVID-19 patients with respiratory distress.

Despite all of these limitations, we believe that HBO_2 therapy warrants further study among COVID-19 patients. The majority of patients with high baseline oxygen requirements arrived for HBO_2 therapy with significant hypoxia based on pulse oximetry. When this occurred they were placed into the hyperbaric chamber. Most patients reported subjectively feeling better while receiving the HBO_2 treatment, with less shortness of breath; and we observed decreased work of breathing in these patients. However, when moved out of the chamber several patients reported a return to experiencing the same symptoms as their pretreatment state, with subsequent hypoxia during transport from the chamber to a wheelchair. Though no patient required advanced airway management in the chamber facility, the post-treatment hypoxia was at times significant and often required high rates of oxygen supplied by high-flow or non-rebreather masks. We cannot overemphasize how unstable COVID-19 patients can be. Safety protocols for monitoring patients during and after transport must be in place before considering HBO_2 therapy for COVID-19 patients.

For infection control, a surgical mask was placed over patients during transport, and all staff had appropriate personal protective equipment (PPE) with N95 masks, face shields, gowns and gloves, in accordance with hospital policy. The treatment team was trained in advanced airway management, along with the donning and doffing of PPE. A clear workflow was established, as these patients require significantly more preparation time in order to safely transfer them in and out of the hyperbaric chamber, which can be associated with oxygen desaturation given the instability of COVID-19 patients. We treated patients seven days a week and did not treat any non-COVID-19 patients, as the unit was considered to carry an infection risk. The chambers, gurneys, and all ancillary equipment were disinfected using standard COVID-19 infection control policies between patients. A deep clean with a bleach solution was sprayed into the chambers and on other equipment and allowed a wet time of at least five minutes, with staff wearing appropriate protection from vapors and no patients present during cleaning.

CONCLUSIONS

Important questions not addressed by this study include how frequently a COVID-19 patient with respiratory distress should be treated with HBO_2 therapy, and what the treatment duration and oxygen pressure should be used. We chose our treatment parameters based on common protocols used in U.S. hyperbaric facilities.

However, these questions need to be answered through further clinical investigations. As our early data suggest that the potential effect size of HBO_2 therapy for patients with COVID-19 could be large, randomized clinical trials should be started immediately.

Finally, HBO_2 therapy is not a widely available therapy. There are approximately 1,400 hyperbaric facilities in the United States, but based on recent surveys only 130 are available for emergencies [30]. Based on our experience so far, it is our opinion that COVID-19 patients should be treated in HBO_2 therapy facilities within a hospital only due to how quickly these patients can deteriorate. Since access to HBO_2 therapy will be limited, there will need to be ethical considerations as to which patients should be placed on these therapies, just as these decisions are being made in the use of ECMO [33]. This limitation of HBO_2 therapy capacity also means that rational public health efforts to prevent transmission must still be considered and efforts to find a vaccine continue to be an important priority.

■

ClinicalTrials.gov Registration: NCT04332081

Author contributions: SG and DL designed the study. DL had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. SG, BG, HL, CA, MO, and DL drafted the paper. BG, HL, CA, MO, CK, and DL collected the data. SA, CK, and DL did the analysis, and all authors critically revised the manuscript for important intellectual content and gave final approval for the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Acknowledgments

This study was funded by internal research support from the NYU Grossman School of Medicine. Dr. David Lee is also funded by grants K23-DK110316 and R01-DK124400, both from the National Institutes of Diabetes and Digestive and Kidney Diseases for unrelated work. All authors of this study have no financial interests in hyperbaric oxygen therapy nor any other relevant financial interests to disclose. Dr. Peter Speigler and Dr. Sarun Thomas at NYU Winthrop have since joined the study team to provide guidance and expertise in pulmonary and critical care medicine.

We want to specifically thank Mike Merrow and Glen Butler at Life Support Technologies, which is a third-party supplier of the hyperbaric chambers at NYU Winthrop and without whom the study would not have been possible. In addition, we want to thank our hyperbaric technologists, Daniel Hennig, Vanessa Newman, John Reynolds, and Heather Quiroz, who bravely volunteered and took on the risk of being exposed to COVID-19 to treat the patients in the study. In addition, we also want to thank Dr. Alan Katz, whose encouragement helped to make this study possible. The above-listed individuals were not involved in the study design, data collection, analysis, or review of the drafted manuscript.

REFERENCES

1. Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. JAMA. 2020 Apr 6; 323(16):1574-1581.

2. Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. JAMA. 2020 Mar 19;323(16):1612-1614.

3. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033-1034.

4. Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Di Napoli R. Features, evaluation and treatment coronavirus (COVID-19). In: StatPearls. Treasure Island (FL) 2020 Jan.

5. Graham RL, Donaldson EF, Baric RS. A decade after SARS: strategies for controlling emerging coronaviruses. Nat Rev Microbiol. 2013;11(12):836-848.

6. Shah RD, Wunderink RG. Viral pneumonia and acute respiratory distress syndrome. Clin Chest Med. 2017;38(1):113-125.

7. Mathieu D, Marroni A, Kot J. Tenth European Consensus Conference on Hyperbaric Medicine: recommendations for accepted and non-accepted clinical indications and practice of hyperbaric oxygen treatment. Diving Hyperb Med. 2017;47(1): 24-32.

8. U.S Food and Drug Administration. Hyperbaric oxygen therapy: don't be misled. August 23, 2013; https://www.fda.gov/consumers/consumer-updates/hyperbaric-oxygen-therapy-dont-be-misled. Accessed May 11, 2020.

9. Thom SR, Keim LW. Carbon monoxide poisoning: a review epidemiology, pathophysiology, clinical findings, and treatment options including hyperbaric oxygen therapy. J Toxicol Clin Toxicol. 1989;27(3):141-156.

10. Butler GJ, Al-Waili N, Passano DV, et al. Altitude mountain sickness among tourist populations: a review and pathophysiology supporting management with hyperbaric oxygen. J Med Eng Technol. Apr-May 2011;35(3-4):197-207.

11. Benson RM, Minter LM, Osborne BA, Granowitz EV. Hyperbaric oxygen inhibits stimulus-induced proinflammatory cytokine synthesis by human blood-derived monocyte-macrophages. Clin Exp Immunol. 2003 Oct;134(1):57-62.

12. MacKenzie DA, Sollinger HW, Hullett DA. Role of CD4+ regulatory T cells in hyperbaric oxygen-mediated immune nonresponsiveness. Hum Immunol. 2000;61(12):1320-1331.

13. Bosco G, Vezzani G, Mrakic Sposta S, et al. Hyperbaric oxygen therapy ameliorates osteonecrosis in patients by modulating inflammation and oxidative stress. J Enzyme Inhib Med Chem. 2018 Dec;33(1):1501-1505.

14. Rossignol DA. Hyperbaric oxygen treatment for inflammatory bowel disease: a systematic review and analysis. Med Gas Res. 2012;2(1):6.

15. Weaver LK, Churchill S. Pulmonary edema associated with hyperbaric oxygen therapy. Chest. 2001;120(4):1407-1409.

16. Abel FL, McNamee JE, Cone DL, Clarke D, Tao J. Effects of hyperbaric oxygen on ventricular performance, pulmonary blood volume, and systemic and pulmonary vascular resistance. Undersea Hyperb Med. 2000;27(2):67-73.

17. Obiagwu C, Paul V, Chadha S, Hollander G, Shani J. Acute pulmonary edema secondary to hyperbaric oxygen therapy. Oxf Med Case Reports. 2015;2015(2):183-184.

18. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet (London, England). 2020;395(10229):1054-1062.

19. Naval Specialty Medical Center Program Team. Demonstration report on inclusion of hyperbaric oxygen therapy in treatment of COVID-19 severe cases. https://www.ihausa.org/Hyperbaric_oxygen_therapy_in_the_treatment_ofCOVID-19_severe_cases.pdf.

20. Thibodeaux K, Speyrer M, Raza A, Yaakov R, Serena TE. Hyperbaric oxygen therapy in preventing mechanical ventilation in COVID-19 patients: a retrospective case series. J Wound Care. 2020 May 1;29(Sup5a):S4-S8.

21. Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol. 2020.

22. Simonnet A, Chetboun M, Poissy J, et al. High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. Obesity (Silver Spring) 2020.

23. Burnand B, Kernan WN, Feinstein AR. Indexes and boundaries for "quantitative significance" in statistical decisions. J Clin Epidemiol. 1990;43(12):1273-1284.

24. Austin PC, Fine JP. Propensity-score matching with competing risks in survival analysis. Stat Med. 2019;38(5):751-777.

25. Wynants L, Van Calster B, Bonten MMJ, et al. Prediction models for diagnosis and prognosis of covid-19 infection: systematic review and critical appraisal. BMJ. 2020 Apr 7; 369:m1328.

26. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA. 2020.

27. Wadhera RK, Wadhera P, Gaba P, et al. Variation in COVID-19 hospitalizations and deaths across New York City boroughs. JAMA. 2020.

28. Hantoushzadeh S, Shamshirsaz AA, Aleyasin A, et al. Maternal death due to COVID-19 Disease. Am J Obstet Gynecol. 2020 Jul; 223(1):109.e1-109.e16.

29. Bessereau J, Aboab J, Hullin T, et al. Safety of hyperbaric oxygen therapy in mechanically ventilated patients. Int Marit Health. 2017;68(1):46-51.

30. Chin W, Jacoby L, Simon O, et al. Hyperbaric programs in the United States: Locations and capabilities of treating decompression sickness, arterial gas embolisms, and acute carbon monoxide poisoning: survey results. Undersea Hyperb Med. 2016;43(1): 29-43.

31. Weaver LK, Wilson SH, Lindblad AS, et al. Hyperbaric oxygen for post-concussive symptoms in United States military service members: a randomized clinical trial. Undersea Hyperb Med. 2018;45(2):129-156.

32. Thomas LE, Bonow RO, Pencina MJ. Understanding observational treatment comparisons in the setting of coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020 May 5.

33. Prekker ME, Brunsvold ME, Bohman JK, et al. Regional planning for extracorporeal membrane oxygenation allocation during coronavirus disease 2019. Chest. 2020.

✦