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Hyperbaric Oxygen Therapy Efficacy as an Adjuvant for the Systemic Inflammation Reduction in Patients with SARS-CoV-2 Infection

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Research Article

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ABSTRACT

Aim: Coronavirus Disease 2019 (COVID-19) is a pandemic caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2). Despite isolation measures, social distancing, and massive vaccination campaigns, the number of people affected by the current COVID-19 pandemic is growing daily. Since no definitive treatment has been identified, preventive and supportive strategies remain the treatment mainstay. Support measures such as oxygen therapy with a nasal cannula, mask, noninvasive ventilation, mechanical ventilation, and even extreme measures such as extracorporeal membrane oxygenation fail to improve oxygenation in some patients. **Objective:** Investigate whether Hyperbaric Oxygen Therapy (HBOT) mitigates systemic tissue inflammation in COVID-19 patients. Serum levels of troponin, ferritin, D-dimer, C-reactive protein, and Lactate Dehydrogenase (LDH) were determined at the beginning and the end of the trial.
Results: Patients were randomly assigned to a control group (without HBOT) or to a group that received therapy (HBOT). In the HBOT group, patients breathed 100% oxygen through closed-circuit masks during three 30-minute periods, while compressed air was administered during 5-minute rest intervals. Treatment lasted ~130 min per HBOT session.
Conclusion: All inflammation markers tested were significantly lower for the HBOT group when compared to the without HBOT group at the end of the study.

INTRODUCTION

In December 2019, an atypical respiratory illness threatened the city of Wuhan, China, and would later become a worldwide pandemic caused by a coronavirus named SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) [1,2]. Meanwhile, the disease caused by SARS-CoV-2 would be called coronavirus 2019 or COVID-19 (Corona Virus Disease 2019) [2,3]. Despite many preventive public health measures (isolation, social distancing, use of face masks, etc.), the high percentage of the population vaccinated, and advances in disease management as such, COVID-19 continues to represent a serious health threat as of February 2, 2022, a total of 381,315,125 confirmed cases and 5,685,892 deaths from COVID-19 have been reported [4,5]. In Mexico, by January 31, 2022, 4,942,590 cases and 306,091 deaths have been reported, and these numbers increase continuously [4,6]. Seemingly most COVID-19 patients develop a mild or moderate form of the disease, including even some asymptomatic cases. However, those patients that develop a severe condition are at a high risk of death and may require hospitalization.

An urgent need to optimize the available treatments for COVID-19 arises, even more so because certain risk factors such as age, comorbidities like diabetes mellitus, arterial hypertension, obesity, and smoking contribute to increasing the severity and mortality of the condition [7]. The high incidence of chronic-degenerative diseases in the Mexican population might predispose COVID-19 patients to a severe illness [8,9], and therefore, novel, and ingenious research is warranted.

Even though vaccines are a significant leap in the battle against the virus, no specific pharmacological therapy to treat the illness has been found yet. Currently, COVID-19 patient management is basically a symptomatic treatment intended to mitigate complications [2,10]. Within non-pharmacological treatment, oxygen supplementation strategies are of great importance, and in extremely severe cases, intubation may be necessary [10]. Notwithstanding, mechanical ventilation carries serious risks and sequelae, and therefore alternative, less invasive therapies, such as Hyperbaric Oxygen Therapy (HBOT), are becoming attractive alternatives. HBOT is administered in specialized chambers that provide 100% oxygen to the patient at an Absolute Atmospheric Pressure (ATA)>1, generally between 1.5-3 ATA, with an average duration of 60-120 min [8,11-13]. It has been recognized that this therapy offers significant anti-inflammatory effects and facilitates the reversal of tissue hypoxia [8,11-13]. HBOT benefic potential in managing of COVID-19 patients is currently being investigated with promising results: it improves symptoms and blood oxygen saturation, reduces inflammatory markers, and significantly lowers the need for mechanical ventilation [8,14-18]. Some studies evaluated inflammatory markers to assess the anti-inflammatory effects of HBOT in patients with COVID-19; troponin, ferritin, D-dimer, C-reactive protein, lactate dehydrogenase, and white blood cell count were some of the parameters evaluated [16-18]. These studies´ results are promising even though they have been limited by the size of the sample. HBOT's potential to mitigate the inflammatory process and avoid mechanical ventilation in severely ill patients represents a feasible alternative therapy. Because of the reasons as mentioned above, we evaluated if HBOT modified inflammation in COVID-19 Mexican patients with diverse concomitant health risk factors (diabetes, hypertension, smoking, and HIV).

MATERIALS AND METHODS

Patients and treatment

The design of this study was a randomized clinical/scientific study with each participant randomly assigned either into the interventional group or the control group.

A total of 78 patients diagnosed with moderate to severe COVID-19 (50 men and 28 women; mean age, 55.1 ± 1.7 years; age range, 25-92 years) received medical care at the Naval Specialties Hospital (Veracruz, Mexico) between June and September 2020. They were subjected to be HBOT to determine its efficacy to improve hypoxemia. Patients were diagnosed by detecting SARS-CoV-2 nucleic acid by positive fluorescence-based Reverse Transcription-quantitative PCR (RT-qPCR) performed at the State Laboratory of the Veracruz Health Ministry (Veracruz, Mexico). The standard treatment administered in the Veracruz Hospital Naval de Especialidades which all patients in the study received is the following: paracetamol 1 g/6 h, vitamin C 1 g/8 h, and acetylcysteine 300 mg/6 h for up to 5 days, in addition to dexamethasone 6 mg/8 h, azithromycin 500 mg/24 h, and ceftriaxone 1 g/12 h for 14 days. It is worth mentioning that patients with comorbidities received their previously established treatment. The present study was approved by the Institutional Bioethics Committee of the Veracruz Hospital Naval de Especialidades HOSNAVESVER/CI/01/2020. It was carried out according to the principles described in the Declaration of Helsinki. The participants gave their informed consent in writing before the study. The patients included in the study, regardless of their gender or age, were diagnosed with COVID-19. In addition, some of the patients had hypertension, diabetes, HIV, were overweight, or were smokers. A complete clinical evaluation was performed on candidates to undergo HBOT. The exclusion criteria were the following: i) refusal to participate and/or refusal to sign an informed consent to receive HBOT; ii) acute congestive heart failure; iii) claustrophobia; and iv) pneumothorax.

In addition to the pharmacological treatment, participants received a daily session of HBOT for 10 days in a multi-place hyperbaric chamber. On average, treatment started 4 days after the initial onset of symptoms. Patients were transferred from hospitalization to the hyperbaric chamber through an exclusive controlled circuit for hospitalized COVID patients. Prior to the transfer, vital signs and quantification of oxygen saturation were evaluated in room air and with respiratory support equipment in case of emergency. An evaluation of the NEWS scale was also carried out to ensure the adequate conditions of the patient to be transferred (to have a parameter of risk of clinical deterioration and adverse events. Scores between zero and two are equivalent to low/medium risk; if the patient meets the low-risk criteria, the blue code would be activated, and PaO_2/FiO_2 would be assessed). In addition to achieving significant improvement in oxygen saturation and symptomatology, HBOT has been shown to decrease inflammation, as evidenced by cabinet markers of inflammation. At the beginning and the end of the trial, serum levels of ferritin, D-dimer, C-reactive protein, Erythrocyte Sedimentation Rate (ESR) and Lactate Dehydrogenase (LDH) were determined at the State Laboratory of the Ministry of Health of Veracruz (Veracruz, Mexico). They were used as prognostic indicators to evaluate the treatment of patients with COVID-19 submitted or not to HBOT. In the State Laboratory of the Veracruz Health Ministry (Veracruz, Mexico) the methods for the inflammatory marker values were the following: D-dimer (inmunolite 2000, chemiluminescence), ferritin (inmunolite 2000, chemiluminescence), DHL (enzymatic method, inmunoturbidimetrico), CRP (plate agglutination) and ESR (direct sedimentation with EDTA). The following values were taken as reference, normal values: d-dimer (287-855 ng/ml),

ferritin (28-397 µg/l in men and 6-159 µg/l in women), DHL (100-190 IU/L), CRP (<6.0 mg/l) and ESR (<10 mm/h). During HBOT, patients were provided with a mask that was part of a closed circuit that delivered a continuous flow of 100% oxygen. They were afterwards introduced in the corresponding hyperbaric chamber. The chamber inlet was sealed and the HBOT session started with a compression (descent) of ~15 min until isopressure (down; 2.0 ATA) was reached and maintained for 90 min, with intervals of 30 min and two 5 minimum rest intervals (8). Subsequently, a decompression (ascent) period of ~15 min was started. During three 30-minute periods, patients breathed 100% oxygen through closed-circuit masks, while compressed air was administered during 5-minute rest intervals. Treatment lasted ~130 min per HBOT session. In the end, the PaO_2/FiO_2 was assessed again, and vital signs were recorded in the data collection and follow-up sheet for each patient. The blue code was activated for the patients´ transfer to hospitalization if they were stable. In case of any adverse event due to transfer desaturation with PAFI/SAFI<100 or clinical deterioration, patients would have been sent immediately to the emergency room for immediate attention. The possible adverse effects were nasal irritation, epistaxis, anxiety, dizziness, headache, increased symptoms, and seldom cerebral arterial embolism, barotrauma, pneumothorax, and sudden death. No major adverse effects were presented during or at end of the study following HBOT.

Statistical analysis

All data were analyzed by GraphPad Prism® version 3.10 (GraphPad Software, Inc.). Paired Student's t-test was used to compare differences before and after HBOT in the same group. The control group without HBOT was evaluated in the same manner. Unpaired Student's t-test was carried out to compare differences between groups with or without HBOT at the beginning and the end of the HBOT period. Data are represented as the mean ± standard error of the mean in the text and graphs. $P<0.05$ was considered statistically significant.

RESULTS

Patients´ generalities

78 patients diagnosed with COVID-19 agreed to participate in the present study that was carried out at the Veracruz Specialty Naval Hospital. All patients received standard pharmacological treatment approved by the Naval Hospital of Specialty of Veracruz and were randomly divided into two groups. The first group did not receive HBOT treatment (without HBOT), while the second group did (HBOT). 10 patients died during the study development; therefore, data for the remaining 68 patients are reported herein. The 10 mortality cases occurred between admission to the study and the first HBOT session with 6 patients belonging to the HBOT group and 4 patients in the without HBOT group. Since these 10 patients were unable to complete the protocol, they were not included in the final results, and the causes for the mortalities were the following: acute respiratory failure, cardiac complications (acute myocardial infarction, acute heart failure) and metabolic acidosis.

The demographic characteristics were similar in both groups: the total number of patients in the HBOT group was 42 patients (29 men, 13 women), and without HBOT 36 patients (21 men and 15 women). The mean age was 53.3 ± 2.17 years (25-92 years) in the HBOT group and 57.22 ± 2.68 years (26-82 years) in without HBOT. The means of weight, height and BMI were: HBOT (78.54 ± 2.17 kg; 1.65 ± 0.01 m and 28.45 ± 0.01 kg/m^2 respectively) and without HBOT (74.63 ± 1.56 kg; 1.65 ± 0.01 m and 27.34 ± 0.42 kg/m^2 respectively). Comorbidities were as

follows: diabetes mellitus type 2 HBOT (25) and without HBOT (14); arterial hypertension HBOT (17) and without HBOT (12); smoking HBOT (12) and without HBOT (10) and HIV HBOT (2) and without HBOT (2) (Table 1).

Table 1. Demographic characteristics of patients with COVID-19, with HBOT and WITHOUT HBOT. BMI=Body Mass Index, HIV=Human Immunodeficiency Virus.

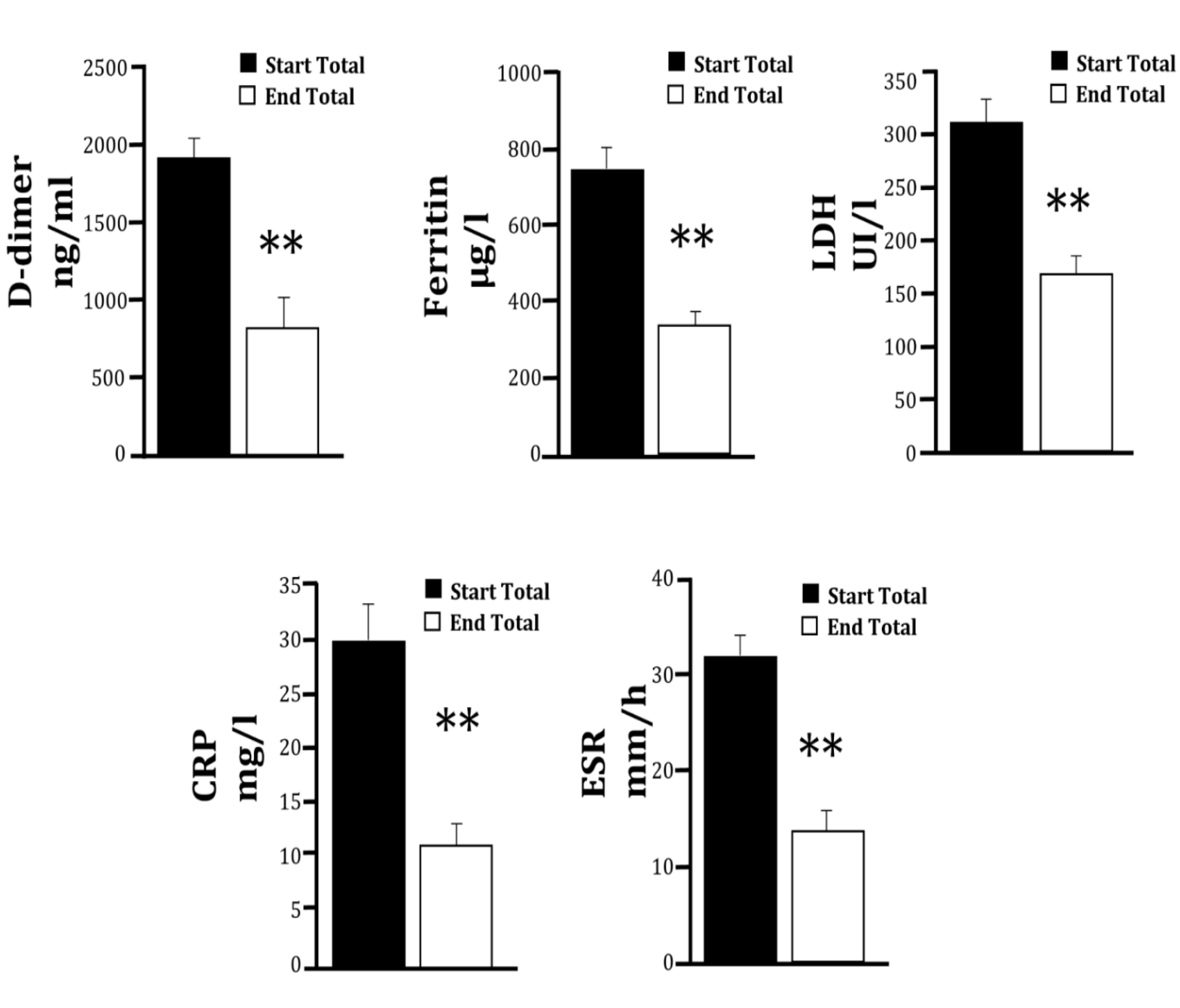
Characteristics	Average value without HBOT	HBOT
Men	21	29
Women	15	13
Age	57.22 ± 2.68	53.3 ± 2.17
Height	165 ± 0.01	1.65 ± 0.01
BMI	27.34 ± 0.42	28.45 ± 0.012
Diabetes Mellitus	Yes (14)	Yes (25)
	No (22)	No (17)
Arterial Hypertension	Yes (12)	Yes (17)
	No (24)	No (25)
Smoking	Yes (10)	Yes (12)
	No (26)	No (30)
HIV	Yes (2)	Yes (2)
	No (34)	No (40)

Analysis of global inflammatory markers at the beginning and the end of the study

Serum inflammatory markers were evaluated at the beginning and the end of the study in all 68 patients. These values were compared as described in "Statistical analysis" section. Inflammatory markers used were D-dimer (ng/ml), ferritin (µg/l), lactic dehydrogenase (DHL, IU/L), C-reactive protein (CRP, mg/l) and erythrocyte sedimentation rate (ESR, mm/h).

The following results in parenthesis are the values before and after the period equivalent to treatment for the whole population tested. For D-dimer (1952.23 ± 129.70 vs. 839.34 ± 201.70 ng/ml), ferritin (751.41 ± 53.55 vs. 345.83 ± 33.31 µg/l), DHL (301.7 ± 21.52 vs. 164.28 ± 16.24 IU/L), CRP (29.4 ± 3.21 vs. 11 ± 2 mg/l) and ESR (32.22 ± 2.07 vs. 14 ± 2.0 mm/h). Paired Student's t-test revealed a highly significant difference ($p<0.01$) for all inflammatory markers when comparing values in the beginning and the end of the protocol (Figure 1).

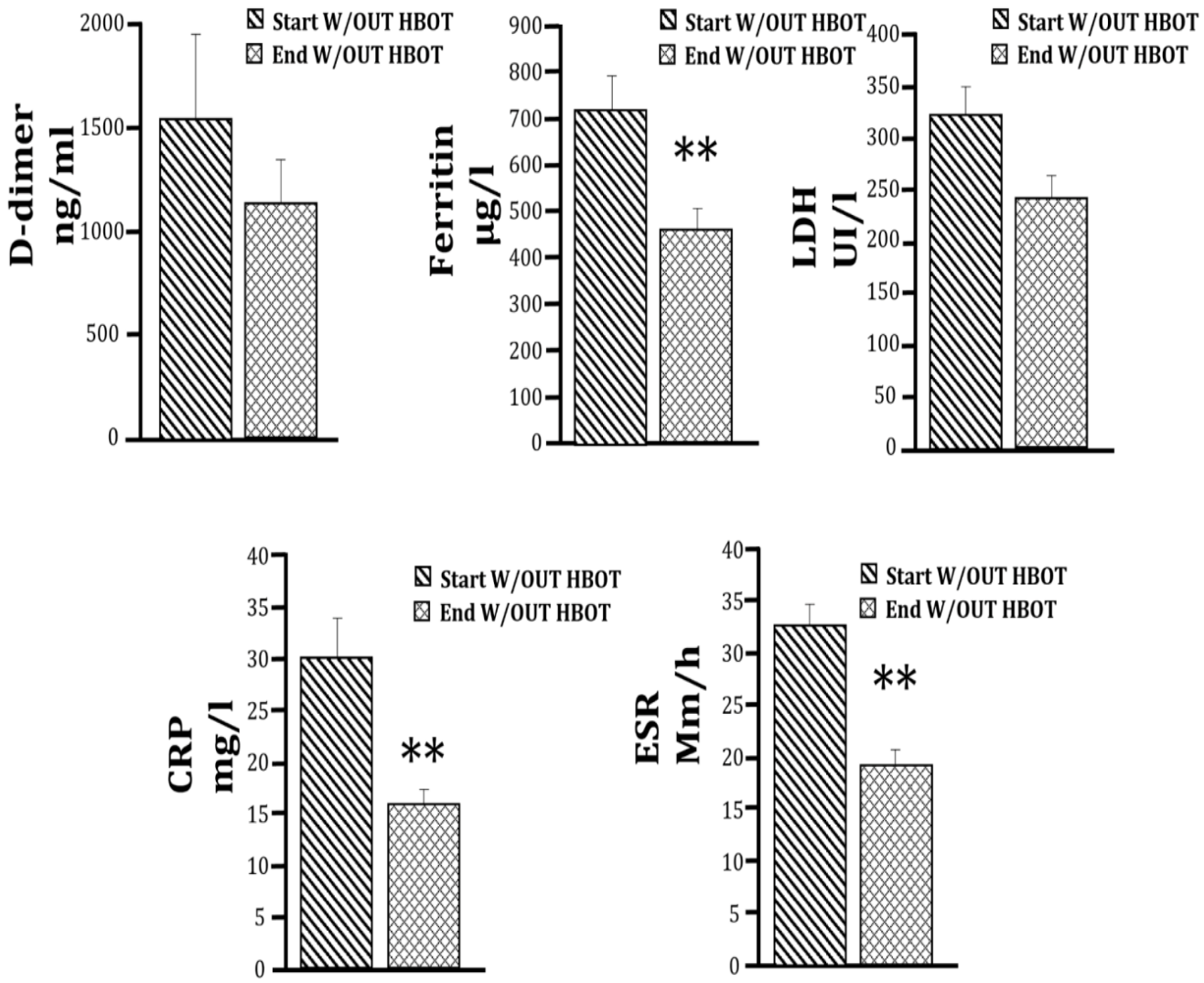
Figure 1. Evaluation of D-dimer (ng/ml), ferritin (µg/l), lactic dehydrogenase (DHL, IU/l), C-reactive protein (CRP, mg/l) and erythrocyte sedimentation rate (ESR, mm /h), at admission and at the end of the study in patients with COVID-19. n=68, **p<0.01 (paired student's t). Bars represent mean ± standard error of the mean. Note: ■: Start total; □: End total.



Difference in inflammatory markers in patients without HBOT at the beginning and at the end of the study

This group, considered as control, was made up by 32 patients that had the following concentrations of the inflammatory markers tested: the averages of the D-Dimer values were (1556.97 ± 408.24 vs. 1148.94 ± 209.35 ng/ml), ferritin (718.38 ± 72.81 vs. 461.1 ± 44.10 µg/ l), DHL (316.25 ± 29.27 vs. 239.88 ± 20.94 IU/L), CRP (29.58 ± 3.86 vs. 15.75 ± 1.41 mg/l) and ESR (32.69 ± 2.04 vs. 19.27 ± 1.47 mm/h). Paired Student's t-test was performed and showed a highly significant difference (p<0.01) for ferritin, ESR, and CRP when comparing values at the beginning and at the end of the trial period (Figure 2).

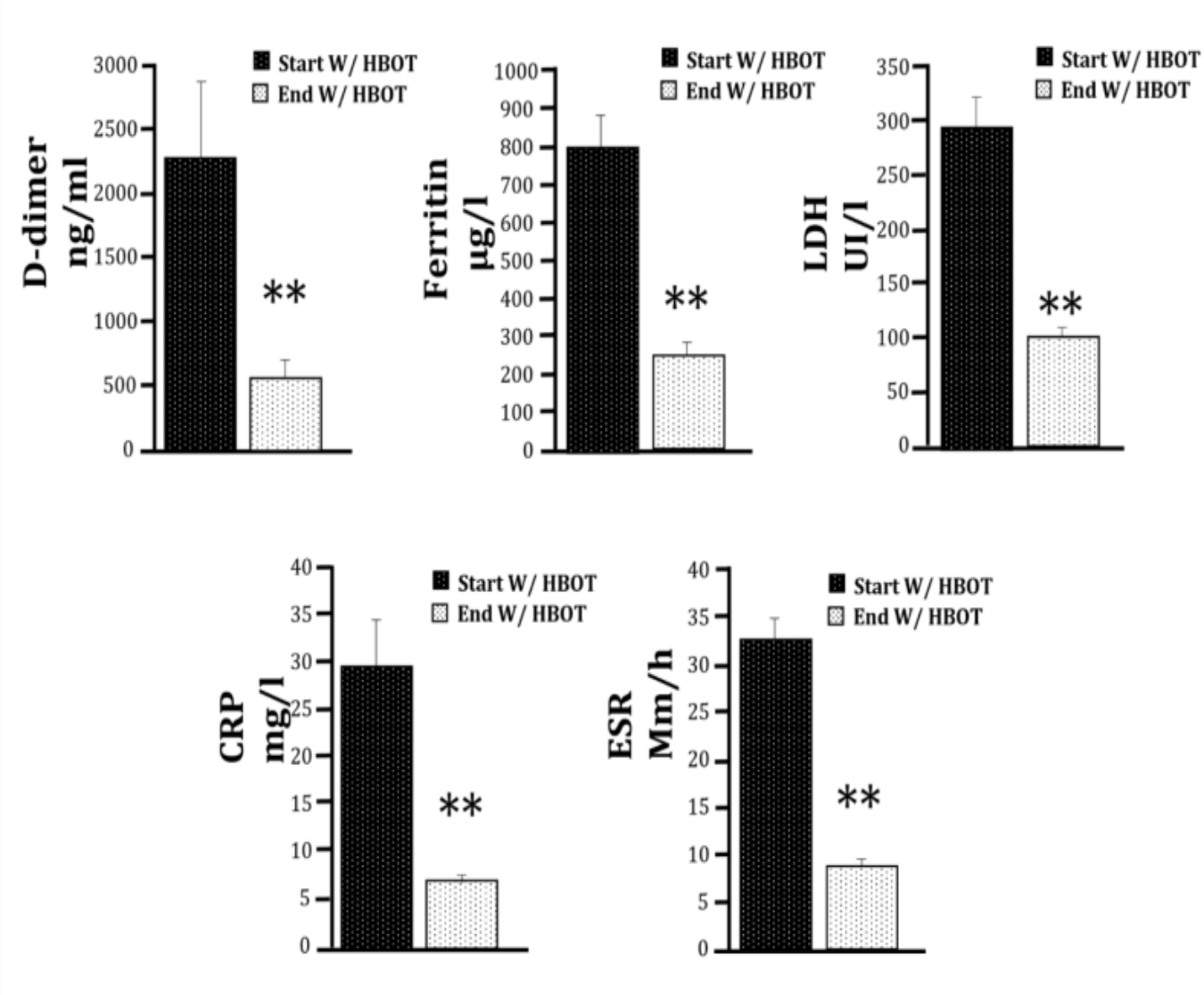
Figure 2. Evaluation of D-dimer, ferritin, Lactate Dehydrogenase (DHL), C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR), at admission and at the end of the study in patients with COVID-19 without HBOT. n=32, **p<0.01 (paired student's t). Bars represent mean ± standard error of the mean. Note: ▨: Start W/OUT HBOT; ▩: End W/OUT HBOT.



Difference in inflammatory markers in HBOT patients at the beginning and at the end of the study

This group comprised 36 patients. The values for D-dimer means were (2291.21 ± 595.09 vs. 573.97 ± 140.35 ng/ml), ferritin (779.71 ± 85.28 vs. 247.02 ± 34.3 µg/l), DHL (289.19 ± 27.02 vs. 99.47 ± 9.45 IU/L), CRP (29.23 ± 5.35 vs. 7.04 ± 0.77 mg/l) and ESR (31.8 ± 2.53 vs. 8.73 ± 0.77 mm/h). Paired Student's t-test was performed and a highly significant difference (p<0.01) for all inflammatory markers was defined (Figure 3).

Figure 3. Evaluation of D-dimer, ferritin, Lactate Dehydrogenase (DHL), C-Reactive Protein (CRP), and Erythrocyte Sedimentation Rate (ESR), at admission and at the end of the study in patients with COVID-19 WITH HBOT. n=36, **p<0.01 (paired student's t). Bars represent mean ± standard error of the mean. Note: ■ : Start W/OUT HBOT; ▨ : End W/OUT HBOT.

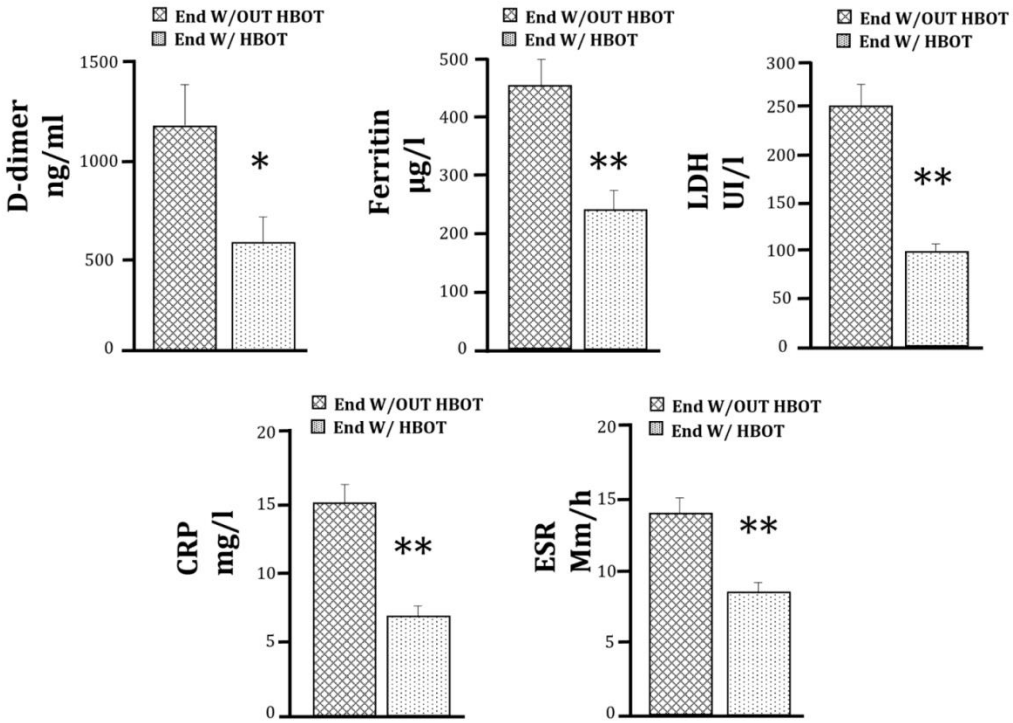


Difference between inflammatory values at the end of the study in patients without and with HBOT

Concentrations of the inflammatory markers obtained at the end of the trial for each group (WITHOUT or WITH HBOT) were compared. Average values for the group WITHOUT HBOT were: D-dimer (1148.94 ± 209.35 ng/ml), ferritin (461.1 ± 44.10 µg/l), DHL (239.88 ± 20.94 IU/l), CRP (15.75 ± 1.41 mg/l) and ESR (19.27 ± 1.47 mm/h). While the HBOT group showed the following concentrations: D-dimer (573.97 ± 140.35 ng/ml), ferritin (247.02 ± 34.3 µg/l), DHL (99.47 ± 9.45 IU/l), CRP (7.04 ± 0.77 mg/l) and ESR (8.73 ± 0.77 mm /h).

An unpaired student's t-test was performed and indicated highly significant differences (p<0.01) for ferritin, DHL, CRP, and ESR, while D-dimer showed a lower significance (p<0.05) (Figure 4).

Figure 4. Comparison of the reference values for D-dimer, ferritin, Lactate Dehydrogenase (DLH), C-Reactive Protein (CRP), and Erythrocyte Sedimentation Rate (ESR), at the end of the study in patients with COVID-19 WITHOUT (n= 32) and WITH HBOT (n=36). *p<0.05, **p<0.01 (unpaired student's t). Bars represent mean ± standard error of the mean. Note: ☒: End W/OUT HBOT; ▩: End W/HBOT.



Difference between the oxygen saturation values at the beginning and the end of the study in patients without and with HBOT

Oxygen saturation levels at the beginning of the study and at the end of the study were compared between the HBOT and without HBOT groups. In the HBOT group, an average of 91 ± 0.72% was obtained at the beginning and 99.13 ± 0.14% at the end of the 10 sessions. In the group without HBOT, an average of 92.59 ± 0.67% was obtained at the beginning and 95.78 ± 0.57% at the end of the study (Table 2).

Table 2. Oxygen saturation values in patients with COVID-19. Oxygen saturation levels were measured at baseline and at the end of the study in the HBOT and NO HBOT groups. The value in the start compared to the end in the HBOT group is highly significant, paired t-Student test, ++p<0.01. However, in the without HBOT group, when comparing the initial and end value it was only significant, paired t-Student test, +p<0.01. When comparing the value at the end of the study in the HBOT group with the end value of the without HBOT group it was also highly significant **p<0.01, unpaired t-Student test. Values in the table express mean ± standard error of the mean.

O_2 Saturation	HBOT	W/OUT HBOT
START	91 ± 0.72	92.59 ± 0.67
END	99.13 ± 0.14++**	95.78 ± 0.57+

DISCUSSION

The results reported herein were in agreement with formerly published results showing that HBOT decreases markers of inflammation such as D-dimer, ferritin, DHL, C-reactive protein, and VS.G. The importance of conducting this study and continuing with this line of research are the additional anti-inflammatory benefits HBOT might provide in the management of patients with COVID-19, given that HBOT plays an essential role in more effective treatments, including long-term anti-inflammatory effects.

The present study demonstrated that HBOT improved inflammatory markers when measured at the endpoint in COVID-19 patients compared to their control group without HBOT. These results are important because few studies in this regard include a control group. In this study, 68 patients were randomly assigned to the control (NO HBOT) or the experimental (HBOT) group.

The demographic characteristics of the patients without HBOT and HBOT coincide with the reported epidemiological data. It is a condition that predominates in the population with a BMI in the range of Overweight and Obesity. The age range was 25-92 years, and the average age of the patients was 55.1 ± 1.77; the comorbidities that were measured, diabetes and AHT, are among the main ones consistently with what is described in the literature [19,20].

Overweight and obesity are a pandemic in themselves. More than 650 million adults worldwide in 2016 were considered overweight or obese, making up about 13% of the adult world population and tripling its prevalence since 1975. Currently, there are more individuals with overweight and obesity than with malnutrition [19]. The disease of overweight occurs when there is an energy imbalance due to excess caloric consumption resulting in a state of metabolic dysfunction [20], implying a health risk predisposing individuals to suffer other diseases, mainly chronic-degenerative ailments such as arterial hypertension, dyslipidemia, type 2 diabetes mellitus, cardiovascular disease, different types of cancer, etc. [21-23]. However, it also represents a risk for infectious diseases because of its deleterious effects on the immune system, making the patient susceptible and increasing the risk of complications, including death [24,25]. It is known that there is a strong correlation between increased BMI and complications from viral infections, specifically SARS and MERS, which are relevant in this case due to the genetic similarity between the SARS-CoV-2 virus and them (80% and 50% respectively) [26,27]. One of the causes of greater infectious susceptibility in patients with increased BMI is due to their chronic inflammatory state that impacts the direct, indirect, and epigenetic immune mechanisms activated by an infectious agent [24,26,28,29]. Energy storing was considered the primary function of adipose tissue; however, nowadays it is known that it has the ability to produce a variety of pro-inflammatory and anti-inflammatory factors, such as adipokines, leptin, adiponectin, resistin, interleukins such as IL-6, TNF-α, MCP-1 [30,31], or amyloid protein A, which directly acts on macrophages to increase the production of TNF-α, IL-1, IL6 and arrestin [26,30,32-34]. High body weight has also been associated with other inflammatory markers such as elevated circulating levels of IL-8, IL-10, IFN-γ, IP-10, and CRP [26,35]. There is a positive association especially between IL-6 and obesity, where up to a third of the total production of circulating IL-6 is attributed to adipose tissue [30,36]. This particular cytokine plays an important role in various inflammatory pathologies, participating in the acute inflammatory response to stimulate the production of C-Reactive Protein (CRP) and fibrinogen from the liver and the release of leukocytes from the marrow [30,37]. When free fatty acids and triglycerides travel to the liver, they promote IL-6 production from the adipocyte, promoting CRP release from the hepatocyte [30,38]. CRP is associated with vascular risk, with each increase of one standard deviation of CRP

increasing vascular risk by 60% [30,38]. It has been observed that, in the immune cell population, a higher BMI is associated with anti-inflammatory CD4 cell populations such as the Th2 and regulatory subgroups [39,40]. During the early stages of the immune response to an infectious agent, an increase in the anti-inflammatory cell population can reduce the ability to fight the pathogen effectively; regulatory T cells are necessary mainly in the late stage in the resolution of post-infectious inflammation [39]. CD4 and CD8 T cells are mobilized to adipose tissue, accelerated by the insulin resistance present in adipocytes and a high-fat diet, and these lymphocytes increase the secretion of cytokines IL-1β, IL-6, IL-8, IL- 10, TNF-α, GM-CSF, promoting the chronic inflammatory state [26,41]. Apart from reducing immune function, obesity favors imbalance in the gut microbiota, promotes the inflammatory cytokine phenotype, and increases antiviral, antimicrobial, and anticoagulant resistance [26]. Given the high prevalence of overweight and obesity worldwide, it is crucial to explore the repercussions that it may have on the pathogenesis and prognosis of COVID-19, considering that the prevalence of obesity among patients hospitalized for COVID-19 can be up to 61.3% [42,43]. Several studies exploring the impact of obesity on the severity of COVID-19; in one study, they explore the relationship between BMI and the need to be admitted to the Intensive Care Unit (ICU), where a clear positive association is observed between a higher BMI and ICU admission, with a 64% greater probability in overweight patients and a 159% greater probability in obese patients [44].

The relationship between obesity and the prognosis for COVID-19 patients was explored In a meta-analysis. Obesity increased the probability of admission to the ICU by 67%, while the risk of dead increased by 37% and the possibility of requiring mechanical ventilation increased by 219%, demonstrating that in all these aspects, obesity impacts the severity of the disease [42]. Popkin, et al. conducted a meta-analysis where a positive association was also observed between a high BMI and an unfavorable outcome in patients with COVID-19: with obesity, the probability of being hospitalized was 213%, the risk of being admitted to the ICU was 74%, the risk of requiring mechanical ventilation was 66%, and the risk of death was 48%. In the Mexican population, the probability of being hospitalized for COVID-19 of a patient with obesity is 64% higher, and the odds of dying are 74% higher. Conceivably, adipose tissue expresses ACE2 and could serve as a reservoir for SARS-CoV-2 or promote its infection. Since obese individuals have increased adipocytes amounts, they might augment the probability for the virus to attach to ACE2, worsening the infection [24,42,45]. One of the main aspects of the pathogenesis of SARS-CoV-2 is the pro-inflammatory state, which increases the risk of severity and mortality in patients with COVID-19 [21,46]. Inflammation can be exacerbated in an obese patient who is already in a chronic inflammatory state. Elevated serum levels of the inflammatory markers IL-1, IL-6, IL-17, IL-18, IFN, and CRP have been found in patients with COVID-19 [21,46,47], even IL-6 has been proposed as a possible marker of severity and progression of the disease [47], which is already elevated in patients with obesity. This pro-inflammatory state and cytokine storm present in COVID-19 and exacerbated by chronic inflammation present in obesity causes acute tissue damage and acute respiratory distress syndrome, the main causes of morbidity and mortality in SARS-CoV-2 infection [39,48].

Currently, there are few studies where HBOT has been shown to decrease inflammation, as demonstrated by laboratory markers of inflammation. For example, Guo et al. evaluated the difference in oxygen saturation levels in patients undergoing HBOT and measured lymphocyte count and found that immune function gradually recovered after HBOT. They also found that D-dimer levels and serum cholinesterase concentrations were improved. In another study, Chen et al. measured lymphocyte count, fibrinogen, and D-dimer levels and found that all these

parameters were significantly decreased after HBOT [49]. Furthermore, Gorenstein et al. evaluated troponin, ferritin, D-dimer, C-reactive protein, and Lactate Dehydrogenase (LDH) levels as prognostic indicators in treating COVID-19 patients undergoing HBOT. At the end of their study, the HBOT-treated group showed a significant improved oxygen saturation and mortality compared to the control group. In another study, procalcitonin and C-reactive protein levels, white blood cell count and differentiation, as well as IL-6, ferritin, D-dimer, and LDH levels, were measured as inflammatory markers. In our study, the HBOT decreased D-dimer, ferritin, DHL, CRP and ESR values to normal or reference values. Contrastingly, none of the values in the WITHOUT HBOT group reached the reference values at the end of the study. Furthermore, inflammatory markers concentrations obtained at the end of the study for HBOT and WITHOUT HBOT groups showed significant differences among them, confirming that HBOT provides benefic anti-inflammatory effects to COVID-19 patients. Our study corroborates that HBOT decreases inflammation, thus promoting recovery in patients with COVID-19 by improving their respiratory symptoms.

CONCLUSION

COVID-19 is characterized by extensive inflammation and involves various tissues depending on the disease severity. Elevated inflammatory markers indicate that the disease has progressed from moderate to severe. Ferritin levels serve to predict the severity and prognosis of patients with COVID-19. HBOT may be a beneficial adjunctive treatment when used in combination with standard pharmacological treatment approved by the Naval Hospital of the Ministry of the Navy in patients with COVID-19. HBOT significantly reduces inflammation and can become an important point in managing the disease. If used at an early stage of the infection, it would significantly improve the respiratory symptoms of patients with COVID-19.

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AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

AUTHORS' CONTRIBUTIONS

SITO analyzed and interpreted the patient data. MCRG, VRA and JCRN recruited patients and performed the hyperbaric oxygen therapy. HSC, LMM, EFS, BS and BSRM analyzed and interpreted the patient data. EC, HSC, LMM and EFS were major contributors in the writing of the manuscript. SITO, EC and EFS confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The present study was approved by the Institutional Bioethics Committee of the Hospital Naval de Especialidades de Veracruz HOSNAVESVER/CI/01/2020, it was carried out in accordance with the principles described in the Declaration of Helsinki. The patients signed their informed consent letter before the study.

PATIENT CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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