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RESEARCH ARTICLE

The Efficacy of Hyperbaric Oxygen Therapy in COVID-19 Patients with Cytokine Storm by Reducing Proinflammatory Cytokine Levels through HSP-70 Regulation: A Systematic Review

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ABSTRACT

SARS-CoV-2 Virus is the causative agent of COVID-19, which is classified as an acute respiratory illness (ARI). The host's Angiotensin Converting Enzyme receptor (ACE2) binds to the SARS-CoV-2 virus spike, initiating the COVID-19 infection. The interaction between this specific binding and Interferon Regulatory Factor 3 (IRF3) initiates the activation of Nuclear Factor Kappa B (NF-kB), leading to the activation of proinflammatory cytokines, including interleukin 6 (IL-6) and tumor necrosis factor-alpha (TNF-α). HSP-70 plays a role in preventing NF-kB from being activated. HBOT reduces proinflammatory cytokines and increases anti-inflammatory HSP-70. This article aims to evaluate and present data on Hyperbaric Oxygen Therapy (HBOT) as a supplementary treatment for COVID-19 patients with cytokine storms. This literature article employs a systematic review methodology that integrates articles and clinical studies from databases including Clinical Trials, Cochrane, Google Scholar, PubMed, ResearchGate, and Science Direct. The search for articles and studies used Boolean. Journals were assessed and synthesized using PRISMA, and inclusion and exclusion criteria were applied— The Joanna Briggs Institute (JBI) Critical Appraisal was used to select the most appropriate studies. Oxygenation using HBOT can inhibit proinflammatory cytokines and NF-kB, increasing Heat Shock Protein-70 in the lungs (HSP-70). HBOT is highly recommended for COVID-19 patients with cytokine storm.

INTRODUCTION

The SARS-CoV-2 virus, one of the viruses that cause acute respiratory infections (ARIs) known as COVID-19, was Initially identified as a novel human disease in Wuhan, China, in late 2019 and has since been disseminated globally. The most distinctive symptoms of pneumonia include a high temperature, myalgia, a dry cough, and chest discomfort (Puspita et al., 2021). Respiratory failure is a major factor, from 1% to more than 7% of the mortality risk associated with COVID-19 (Puspita et al., 2021). In hospital settings, around 15-20% of patients have hypoxaemic respiratory failure and require oxygen treatment. Hyperbaric Oxygen Therapy (HBOT) is an alternate treatment for managing hypoxemia induced by COVID-19. According to previous studies, HBOT has successfully treated all forms of oxygen deprivation. HBOT is a non-invasive procedure that can be used as a primary or adjunctive form of therapy. Empirical evidence has confirmed the efficacy of HBOT in managing several systemic diseases, including diabetic foot ulcers, crush injuries, decompression sickness, carbon monoxide poisoning, and arterial gas embolism (Oliaei et al., 2021; Setianingsih et al., 2018).

HBOT, or hyperbaric oxygen therapy, utilizes of high ambient pressure (over 101.3 kPa, which is equivalent to 1 ATA, which is 760 mmHg). Pressures ranging from 2.4 to 2.8 ATA are utilized in clinical practice for durations ranging from 60 to 120 minutes, with arterial blood oxygen pressures ranging from 1800-2200 mmHg. 100% oxygen is usually used for breathing when patients are exposed to hyperbaric conditions because it has therapeutic benefits on all body tissues and travels through microcirculation to all body tissues (Setianingsih et al., 2018; Siewiera et al., 2022).

SARS-CoV-2 can spread through droplets, aerosols, vomits, animal-to-human contact, mother-to-child contact, fecal-oral contact, and blood contact. The SARS-CoV-2 virus can be transmitted by direct contact with an infected individual or through saliva, respiratory secretions, or respiratory droplets emitted during coughing, sneezing, talking, or singing (Danladi & Sabir, 2021). Acute lung injury is the clinical hallmark of severe COVID-19. Other symptoms include heightened pro-inflammatory cytokines in the blood, a buildup of pulmonary macrophages and neutrophils, and high baseline virus titers (Paganini et al., 2020). This condition triggers a cytokine storm. The cytokine storm produced by the virus is one of the key factors leading to poor outcomes in SARS-CoV infection (Heck et al., 2020).

A brief overview of the steps involved in the inflammatory process caused by the covid virus in humans is as follows: first, the SARS-CoV-2 spike (S) attaches to the angiotensin converting enzyme receptor (ACE2) of human, which initiates the infection of host cells. Then, Interferon Regulatory Factor 3 (IRF 3) occurs, which activates the formation of Nuclear Factor Kappa-light-chain-enhancer of activated B-cells (NF-kB). NF-kB activation will lead to the activation of inflammatory factors, including interleukin 6 (IL-6) and tumor necrosis factor-alpha (TNF-α) (Danladi & Sabir, 2021). To prevent NF-kB from entering the nucleus, HSP70, forms an association with the complex composed of NF-kB and its inhibitor (I-kB). HSP72, HSP73, and HSP78, members of the HSP70 protein family, are chaperones that reduce inflammation and have been shown that the use of drugs to induce HSP70 in anti-inflammatory cyPG can alleviate various inflammatory disorders (Heck et al., 2020; Krihariyani et al., 2021).

There are several therapeutic approaches utilized for COVID-19 treatment today. The treatment method used is tailored to the situation. Antivirals have been authorized by the FDA (Food and Drug Administration) for COVID-19 treatment, ranging from mild to severe cases. Antivirals are targeted to inhibit the transmission the virus throughout the body (CDC, 2023). Remdesivir is one of the antivirals approved by the FDA in adult patients (>12 years) who are hospitalized (HHS, 2023). Ritonavir-Nirmatrelvir can be utilized as oral antivirals for mild to moderate cases of COVID-19. Molnupiravir is an option for non-hospitalized individuals experiencing mild to moderate COVID-19 but have a high likelihood of developing severe symptoms and in the absence of alternative medications (NIH, 2023a; Petty & Malani, 2022). Any patient requiring mechanical ventilation, extracorporeal membrane oxygenation, non-invasive ventilation, or high-flow nasal cannula oxygen should primarily take dexamethasone as an anti-inflammatory (NIH, 2023b). In some cases, patients with weakened immune systems may be given convalescent plasma (CDC, 2023). Antipyretics, analgesics, and antitussives were given for symptom management of COVID-19 patients who complained of headache, myalgia, and dry cough (HHS, 2023). Antiviral drugs have some drawbacks, such as the side effects caused by Paxlovid (nirmatrelvir/ritonavir) of a bitter taste in the mouth, diarrhea, and myalgia.

Oxygenation is a vital component of treating COVID-19 symptoms in patients. One of the oxygenations given to them is called Hyperbaric Oxygen Therapy (HBOT), which is a treatment with 100% oxygen under elevated atmospheric pressure (Latham et al., 2020). The COVID-19 treatment strategy with HBOT is linked to the risk of hypoxemia events. According to prior studies, the intervention group needed a median of 3 days (IQR 1.0-4.5) to recover from hypoxemia, while the control group needed a median of 9 days (IQR 5.5-12.5) ($p < 0.010$). Among the HBO2 group, the odds ratio (OR) for hypoxemia recovery on day 3 was 23.2 (95% CI 1.6 to 329.6; $p = 0.001$); in comparison to the control group, it was noticeably higher. The treatment had no substantial adverse effects on mortality, mechanical ventilation, or acute respiratory distress syndrome within 30 days of hospitalization (Oliaei et al., 2021). Therefore, it is strongly advised that COVID-19 patients experiencing cytokine storm undergo hyperbaric oxygen therapy (HBOT).

In one study, HBOT can increase Heat Shock Protein (HSP) expression in the hypothalamus and lungs (HSP-70). HSP can overcome High-Altitude Exposure (HAE)-induced brain and lung oedema, cognitive impairment weight loss, oxidative stress, decreased food intake, and brain inflammation. HBOT also increases the expression of hippocampus and Heat Shock Protein in the lungs (HSP-70) (Wu et al., 2018).

Therefore, a Systematic Review on the effectiveness of HBOT for COVID-19 patients with cytokine storms is needed to avoid complications that can occur in patients. Although the COVID-19 pandemic status has been revoked in Indonesia based on Presidential Decree No. 17 of 2023, it does not mean that COVID-19 is not a health problem in Indonesia because its status is an endemic disease.

MATERIAL AND METHODS

This research is a systematic review that uses clinical studies that have been conducted or implemented previously. Article searches were conducted online through various scientific databases (such as Cochrane, Science Direct, google scholar, clinical trials, and PubMed) thoroughly and comprehensively (Figure 1). An algorithm search was executed Boolean "AND" or "OR" with "Hyperbaric Oxygen Therapy" AND "COVID-19" AND "cytokine storm" as keywords. PRISMA refers to the acronym Preferred Reporting Items for Systematic Reviews and Meta-Analyses. Research paradigm was utilized to assess and synthesize the outcomes collected from the journals in this Systematic Review.

The search's inclusion criteria were set to papers published between 2019 and 2023 to ensure the articles were current. The articles that were utilized were published in journals on both a national and international scale. In addition, constraints on language were implemented to restrict the search to articles exclusively published in English and Bahasa Indonesia. All relevant papers were screened and assessed based on quality and relevance to the review topic, questions, and objectives to determine inclusion or exclusion from the literature review. Concurrently, the research query matched each article's abstract and title. The entire text of the article was verified for accessibility if the title and abstract corresponded. Ultimately, the researcher thoroughly perused the full content and determined its relevance. The study excluded paid papers and non-English and Bahasa Indonesia content.

The chosen papers will undergo a quality assessment based on each article's inclusion and exclusion criteria, as well as design utilizing the Joanna Briggs Institute (JBI) Critical Appraisal technique. Articles will be categorized into high (> 70%), medium (50%-70%), and low (< 50%) qualities. Both researchers will conduct an article quality assessment. After the quality assessment, the articles will be analysed using descriptive analysis techniques, which involve more in-depth interpretation and explanation of the research findings and their interrelationships through narrative storytelling.

RESULT AND DISCUSSIONS

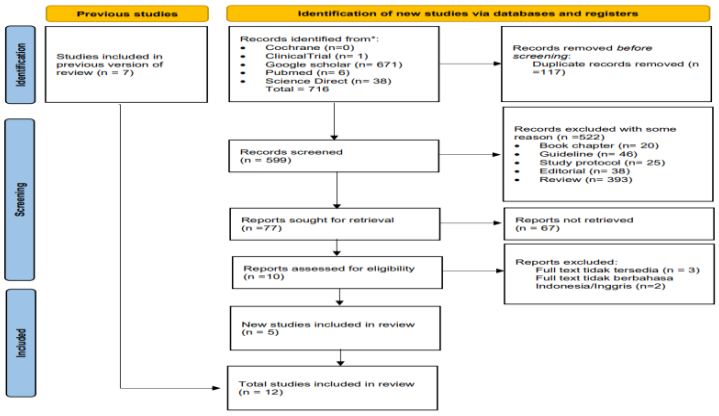

Figure 1. Protocol for selecting articles in the literature review using PRISMA.

DISCUSSION

Through a literature search on five databases, 716 articles were found that were relevant to the keywords used by the researchers. 117 of them were duplicates and 522 articles were excluded because they did not match the study design in the researcher's inclusion criteria. Thus, the remaining 77 articles will be the object of selection based on the overall content of the article. From this selection, 12 articles were found to be in accordance with the research objectives, inclusion criteria, and exclusion criteria, so the articles were included in the study and continued to the study quality assessment stage (Table 1).

Table 1. Study Characteristics

Author, year, location (country)	**Risk of bias**	**Study Design**	**Intervention**	**Patient Characteristics**	**Patient Outcome**	**Conclusion**
Gorenstein, 2020, U.S.	High Quality	Clinical Trial	The pressure of 2.0 atmospheres absolute (ATA) for a duration of 90 minutes.	n=80 a) Intervention group (n=20): HBOT. ● Mean age 58.4 years. ● 18 males (90%), 2 females (10%). b) Control group (n=60): propensity-matched patients. ● Mean age 60.9 years. 55 males (92%), 5 females (8%).	Mechanical ventilation a) n=2 (10%) b) n=18 (30%) Death a) n=2 (10%) b) n=13 (21,7%) Remained hospitalised a) n=0 (0%) b) n= 3 (5%)	● HR for time to death = 0.37 (95% CI from 0.10 to 1.37) ● HR for time to mechanical ventilation = 0.37 (95% CI from 0.10 to 1.37 Adverse effects ● Epistaxis, earache, claustrophobia (n=NR) ● Severe hypoxia (n=1) The results showed the safety of HBOT in COVID-19 patients.
Levina, 2020, Rusia	Medium Quality	Clinical Trial	1,4–1,6 ATA, <60 minutes	n=32, divided into 2 groups based on the severity of CT results: a) n=10, moderately severe. ● Average age 63.5 years. ● 5 male (50%), 5 female (50%)	Both patient groups showed improved blood oxygen saturation and decreased breathlessness.	Daily sessions (at least 4) show safety, and a positive effect on the patient's mental state and the dynamics of blood oxygen saturation.

				b) n=22, serious condition. ● Mean age 59. 10 male (45.5%), 12 female (54.5%)		
Petrikov, 2020, Rusia	Medium Quality	Clinical Trial	1.4-1.6 ATA, 40 minutes	n=87 a) Intervention group (n=57): HBOT. ● Mean age 58.8 years. ● 30 male (52.6%), 27 female (43.3%). b) Control group (n=30): did not receive HBOT. ● Mean age 64.5 years. 13 Males (43.33%), 17 Females (56.67%).	Blood malondialdehyde a) n=57, there was a decrease from 4.34 ± 0.52 µmol/L to 3.98 ± 0.48 µmol/L. n=30, NR	HBOT is an effective treatment method with increased hemoglobin oxygen saturation, decreased lipid peroxidation, activation of the antioxidant system, and normalization of apoptosis in COVID-19 patients.
Thibodeaux, 2020, U.S.	High Quality	Retrospective Case Series	2.0 ATA, 90 minutes	n=5 ● Age 39-63 years old. ● 1 Male (20%), 4 Female (80%).	Patients recovered n=5 (100%). Oxygen saturation is 97% at 45% FiO2 ● Pre-HBOT: 95,5±2,61% ● Post-HBOT: 94,6±2,30% ● After 24 h: 96±1,41% *Respiratory rate* ● Pre-HBOT: 35,4±8,47 Post-HBOT: 28±7,55	HBOT reduces dependence on mechanical ventilation and improves oxygen saturation of COVID-19 patients.
Guo, 2020, China	High Quality	Case Report	1.5 ATA, 60 minutes (1 week)	n=2 ● The patients were 57 and 64 years old. ● 2 Males (100%) Symptoms: shortness of breath, RR >30x/min, SpO2 93% at rest, and	Patients improved n=2 (100%). Post-HBOT: reduced dyspnea, shortness of breath, decreased RR, increased SpO2, serum D-dimer and cholinesterase reflected improved liver function, CT results showed lung inflammation had improved.	HBOT can efficiently accelerate the recovery of hypoxaemia in patients with COVID-19 pneumonia.

				P/F ratio ≤ 300 mmHg.		
Qian, 2020, Cina	Medium Quality	Prospective Case Series	1.5 ATA, 90 minutes (1 week)	n=4 ● Patient age was 56-67 years old. ● 4 Male (100%) Symptoms: dyspnea, CT lung lesion > 30%, SpO2 < 90%.	Patients improved n=2 (100%). Post-HBOT: dyspnoea reduced, SpO2 improved from 86% to 92%, six-minute walk distance increased from 272 m to 346 m, blood gas analysis index (AGD) improved, and CT resolution of inflammation at different degrees.	NA
Liang, 2020, China	High Quality	Case Report	O2 dose 216 UPTD (Units of Pulmonary Toxic Dose), 95 minutes. Considered equivalent to 2.8 ATA.	n=1 ● The patient's age was 69 years. ● 1 Male (100%) Symptoms: chills, body temperature 37.8^{0}C, CT multiple patchy ground glass opacity (GGO)	The patient improved n=1 (100%). Post-HBOT: blood gas examination showed PO2 122 mmHg, PCO2 37.3 mmHg, and SpO2 reached 99%, and CT showed consolidation areas in bilateral lungs decreased.	HBOT directly causes to fulfil the oxygen deficit in hypoxic tissues and organs throughout the body which can provide an optimal basis for the body to systemically fight against viral infections.
Zhong, 2020, China	High Quality	Case Report	1.6-1.8 ATA, 70-100 minutes (4 sessions)	n=1 ● The patient's age was 87 years. ● 1 Male (100%). Symptoms: COVID-19 patient with endotracheal intubation.	Patients improved n=1 (100%). Post-HBOT: improved liver and kidney function, and increased blood clotting.	HBOT significantly reduced carbon dioxide (CO2) build-up in COVID-19 patients.
Siewiera, 2022, Poland	High Quality	Randomized Controlled Trial	2.5 ATA, 60 minutes (5 sessions)	n=28 ● Age 24-78 years ● 23 male (82.1%) and 5 female (17.9%) a) Intervention group (n=14): HBOT. Control group (n=14): did not receive HBOT	Mortality (p=0,067) a) n=0 (0%) b) n=3(21,4%) There was a decrease in CRP, ferritin, and LDH and an increase in CD3 in the HBOT group compared with the control. COVID-19 IgG was higher compared to the control group.	HBOT can reduce inflammation and partially restore T-cell responses.
Hadanny, 2022, Israel	High Quality	Randomized Controlled	2.2 ATA, 60 minutes (8	n=30 a) Intervention group (n=20): HBOT.	Oxygen saturation 97% at 45% FiO_2 ● Pre-HBOT: 89,75 ± 2,67	HBOT can increase oxygen levels in the body, reduce inflammation,

			sessions, 2x/day)	b) Control group (n=10): Received standard medical care (remdesivir, oxygen, steroids, antibiotics, and Low-Molecular Weight Heparin (LMWH)).	● Post-HBOT: 93,78 ± 3,49, p<0,0014 ● Pre-control: 90,44 ± 2,40 ● Post-control: 87,71 ± 7,86, p=0,356 ● *Respiratory rate* ● Pre-HBOT: 28,6 ± 5,5 ● Post-HBOT: 20,1 ± 5,2 (decreased), p<0,0001 ● Pre-control: 25,1 ± 5,3 ● Post-control: 9,8 ± 6,7 (increased), p=0,19 There was a decrease in CRP and LDH in the HBOT group compared to the control group and a higher proportion of COVID-19 IgG antibodies than the control group.	and improve the clinical condition of patients with severe COVID-19. The HBOT protocol can be performed safely and has a low risk of side effects.
Robbins, 2021, England	Medium Quality	Kohort Retrospektif	2.4 ATA, 105 minutes (12 days/10 sessions)	n=10 ● Average age was 47.5 years (24-74 years). ● 4 males (40%) and 6 females (60%). Symptoms were experienced for >3 months.	HBOT resulted in statistically significant improvements in Chalder fatigue scale (p=0.0059; d=1.75), global cognition (p=0.0137; d=-1.07), executive function (p=0.0039; d=-1.06), attention (p=0.0020; d=-1.2), information processing (p=0.0059; d=-1.25) and verbal function (p=0.0098; d=-0.92).	HBOT was significantly beneficial after undergoing 10 sessions.
Cannellotto, 2022, Argentina	High Quality	Randomized Controlled	1.45 ATA, 90 minutes (7 days)	n=39 ● Mean age 55 years. ● Symptoms: dyspnoea, fever, odinophagia. a) Intervention group (n=19): HBOT. Control group (n=20): received standard medical care (antibiotics, steroids,	Baseline oxygen saturation for the whole group 85.1%±4.3% • Post-HBOT: 86.5%±3.9% • Post-control: 84.1%±4.5% In the group receiving HBOT, hypoxaemia was successfully managed (SpO2 level ≥93%), with a more significant increase in arterial saturation compared to the control group.	HBOT is safe and effective in treating COVID-19 and severe hypoxemia conditions.

				antipyretics, and reservoir mask oxygen.		

Based on the research reference table in the appendix, it can be seen that there are 12 articles reviewed, consisting of three clinical trial research articles, two case series research articles, three RCT (Randomized Control Trial) research articles, three case report research articles, and one cohort research article. From the results of the review, each author provides an intervention that is different from one another.

Based on research conducted by Siewiera (2022) and Liang (2020), a dose of 2.4-2.8 ATA for 60-120 minutes is considered effective (Liang et al., 2020; Siewiera et al., 2022). Research conducted by Robbins (2021) is in line with Siewiera, the dose given was 2.4 ATA for 105 minutes (Robbins et al., 2021). Several other studies provide different doses of HBOT. The results of Hadanny's research (2022), had good results with a dose of 2.2 ATA given for 90 minutes (Hadanny et al., 2021). A lower dose was also used by Gorenstein (2020) and Thibodeaux (2020), which was 2.0 ATA for 90 minutes (Gorenstein et al., 2020; Thibodeaux et al., 2020). In the study of Zhang, Guo, Qian (2020), they used a dose of 1.5 ATA from 60 minutes to 100 minutes (Guo et al., 2020; Zhang et al., 2020; Zhong et al., 2020). Other studies conducted by Levina (2020), Petrikov (2020), and Cannellotto (2022), used a dose of 1.4-1.6 ATA for 40 minutes to 90 minutes (Cannellotto et al., 2022; Levina et al., 2021; Petrikov et al., 2021).

From the 12 articles reviewed by researchers, it can be concluded that the highest dose of HBOT is 2.8 ATA and the lowest dose is 1.4 ATA, with relatively different durations. Ranging from 40 minutes to 120 minutes. Each study showed good results in patients, including no hospitalization at the end of the study, increased oxygen saturation, decreased shortness of breath, decreased blood malondialdehyde, decreased respiratory rate, reduced dyspnea, serum D-dimer and cholinesterase describe improved liver function, CT results describe reduced lung inflammation, decreased CRP, ferritin and LDH, and increased CD3.

Based on 12 articles that have been reviewed by researchers, there is only one article that reports cases of death in the intervention group given HBOT. Two hospitalized patients died (10%) from the HBOT intervention group and 13 patients died (22%) from the control group (propensity-matched controls). The inpatient mortality rate was 0.37 (p=0.14) which is not significant.

The exact mechanisms by which SARS-CoV-2 affects the human body are not completely known, however, it is believed to be caused by an excessive immune response. Individuals with severe symptoms of COVID-19 exhibit indications of an unregulated systemic inflammatory reaction known as cytokine release syndrome (CRS), a state that has been identified in cases of SARS and MERS. Before SARS-CoV-2 infecting host cells, the following steps must be taken: the human ACE2 receptor must attach to the spike (S) protein of the virus. Hence, ACE2 serves as the primary objective for vaccination, effectively obstructing the virus's penetration into the host cell (Danladi & Sabir, 2021). During 3- to 14-day incubation, the patient does not show any symptoms, and the numbers of white blood cells and lymphocytes remain within the normal range or may slightly decline. Subsequently, patients start to manifest modest symptoms as the virus spreads via the bloodstream, particularly targeting the organs that generate ACE2. Mild symptoms begin to appear in the patient. The patient's disease shows signs of deterioration between four to seven days subsequent to the initial manifestation of symptoms, as indicated by the presence of dyspnea, reduced lymphocytes, and increasing lung lesions. If this stage is not addressed, it might result in complications, including sepsis, acute respiratory distress syndrome (ARSD), and others. Concomitant diseases, including obesity, hypertension, chronic obstructive pulmonary disease (COPD), and diabetes, as well as age greater than 70 years, are linked to more severe clinical manifestations (Fitriani, 2020).

The influx of viruses and bacteria infecting the body leads to the formation of NF-kB and IRF, which leads to the production of type 1 IFN and pro-inflammatory cytokines, IL1, IL-6, IL-12, and TNF-α (Danladi & Sabir, 2021; Fitriani, 2020). Increased levels of proinflammatory cytokines substantially effect the morbidity and mortality rates linked to SARS-CoV-2 infection. NF-kB expression was increased in the lung epithelium of deceased COVID-19 patients, which was also characterized by the presence of edema,

pulmonary inflammation, and damaged epithelial layers (Attiq et al., 2021). In COVID-19, the onset and progression of acute respiratory distress syndrome (ARDS) are greatly influenced by inflammatory cytokine storms. In ARDS patients, serum cytokine levels were considerably elevated, and the extent to which these levels were elevated was positively associated with death. Extrapulmonary multiple organ failure is greatly influenced by cytokine storm in its clinical progression (Ye et al., 2020).

Mitogen-activated protein kinase (MAPK) activation is initiated by the presence of free radicals, and hydrogen peroxide. Hydrogen peroxide modulates signal transmission by inhibiting phosphoinositide 3-kinase (PI3K), consequently deactivating proapoptotic proteins and activating transcription factors that regulate the synthesis of antiapoptotic proteins. This process could allow the cell to enhance its ability to survive. In addition to having an impact on antiapoptotic proteins, hydrogen peroxide will also regulate MAPK activation, which will also help cells to be able to increase survival, growth, and cell differentiation (Suyono, 2018). One study showed a correlation between an increase in MAPK and an increase in HSP-70. Several studies have shown that MAPKs are one of the factors that lead to the regulation of HSP-70 (Demertzioglou et al., 2021). The activity of MAPK will inhibit NF-kB activation through HSP-70 expression (Wang et al., 2017). The use of HBOT therapy has been shown to increase ROS. Increased ROS will induce antioxidant enzyme activity, thereby suppressing oxidative stress and tissue and cellular damage (Krajcovicova & Meluš, 2014). Indirectly, HBOT will increase the production of free radicals / ROS but on the other hand, can activate the release of HSP-70.

Extracellular heat shock protein 70 (HSP-70) is crucial in controlling innate immunity and activating cell—and organismal-level endogenous protective processes in animals, based on studies that have been conducted in vivo and in vitro. HSP-70 is present in cells in a typical physiological state (Sulistyowati et al., 2018). HSP are a collection of stress proteins that are responsible for protecting cells and tissues against various cytotoxic responses and can be a primary regulator of the host immune system (Wang et al., 2017).

Apart from the MAPK pathway that can increase HSP-70, there are other pathways that can increase HSP-70. The increase in human body temperature when infected with the COVID-19 virus is the result of proinflammatory cytokines induced by an increase in NF-kB (Danladi & Sabir, 2021).

Managing COVID-19 patients with cytokine storm involves administering antiviral medications to hinder the reproduction of SARS-CoV-2. Additionally, possible consequences such as cytokine storm are managed by employing suitable immunosuppressive and immunomodulatory therapies to decrease systemic inflammation. The most frequently employed treatments for cytokine storms are corticosteroids and targeted therapies, particularly IL-6 receptor antagonists such as tocilizumab (TCZ) and IL-1 antagonists like anakinra. Patients with severe clinical conditions (e.g. persistent fever, respiratory failure, CT scans with 50% poor picture) require corticosteroids. The duration of dexamethasone is usually used for 7 days at 1-2 mg/kg/day. The dosage can be reduced to 6 mg per day promptly upon showing signs of improvement. Dexamethasone exhibits a prolonged half-life (Soy et al., 2021).

Antiviral medicines have demonstrated efficacy in shortening the duration of treatment and enhancing clinical results in severe COVID-19 patients. Baricitinib is an antiviral that acts as a JAK/STAT pathway inhibitor. Inhibiting this pathway will limit the excessive immune response known as cytokine storm, hence decreasing the entry of SARS-CoV-2. The dose of baricitinib is 2-4 mg/day. Lopinavir (400 mg dose) and Ritonavir (100 mg dose) are antivirals that function to increase antiviral immunity (Yousefifard et al., 2020).

The use of antiviral agents should be considered with caution in patients with cytokine storm as it may worsen systemic inflammation. Therefore, the use of antiviral agents should be combined with appropriate anti-inflammatory treatment to reduce systemic inflammation and control cytokine storm (Soy et al., 2021; Yousefifard et al., 2020).

The use of Hyperbaric oxygen therapy (HBOT) for antiviral therapy still requires further research. Previous studies have reported that the relationship between HBOT and viral replication is uncertain. However, there is literature that suggests viral infection does not induce the release of oxidative stress, but host defences

that induce ROS counteract the effects of the virus. ROS react with phospholipids from the host, while phospholipids together with proteins found in the host are used by the virus to form the capsid (envelope). HBOT utilization among patients with viral diseases, such as COVID-19, is associated with increased ROS production. Therefore, it is reasonable to test HBOT to reduce viral load or inhibit viral replication (Paganini et al., 2020). However, studies conducted by Guo (2020) and Siewiera (2020) who examined the use of HBOT for COVID-19 and pneumonia patients proved effective with the results of changes in patients' CT results (Guo et al., 2020; Siewiera et al., 2022).

Hyperbaric therapy does not cause oxygen toxicity to the body if given at a dose that is appropriate to the patient's condition. This is commensurate with the hormesis theory which states that at low doses, substances containing "toxins" can have beneficial effects, while at high doses they cause inhibitory or destructive effects on cells and tissues. This hormesis theory is biphasic and can be found in the response of organisms and cells to phytochemicals. Adaptive responses in cells have 3 main cellular defence systems, namely protection against reactive oxygen species by antioxidants, repair of DNA with double-strand breaks, and elimination of damaged cells by apoptosis. The cellular defence system is an adaptation process carried out by cells called hormetic response upon adequate exposure. One form of cell adaptive response after ROS exposure is the formation of heat shock protein (HSP) (Lee et al., 2014; Shibamoto & Nakamura, 2018).

Hyperbaric Oxygen Therapy (HBOT) is widely used as a supportive therapy or adjuvant therapy for various diseases, one of which is COVID-19 infectious disease. In one study conducted by Siewiera (2020), it showed that HBOT correlated with a decrease in inflammatory response (Siewiera et al., 2022). In addition, according to Gorenstein (2020), hyperbaric oxygen therapy is considered safe to use for patients infected with COVID-19 (Gorenstein et al., 2020). The outcomes of this investigation are consistent with Levina's research (2020), which shows that daily sessions of providing excessive oxygen therapy in a "soft" state, which, as an intricate COVID-19 therapy, is at least four times as strong as the standard, with a pressure of 1.4–1.6 ATA, shows the safety of therapy and the therapy is considered to have a positive effect on mental state and oxygen saturation checked through the patient's blood (Levina et al., 2021). The advantage of this therapy is the delivery of oxygen at high partial levels, allowing oxygen to reach the tissues very quickly. Administering hyperbaric oxygen therapy (HBOT) to COVID-19 patients experiencing acute hypoxia can elevate the oxygen levels in the arteries. As supportive therapy, HBOT has advantages compared to ventilators, oxygen can reach cells in the tissue, and induce 2 transcription factors, namely Nrf-2 which has the role of stimulating the production of hundreds of cell defense proteins that mostly function in oxidative stress response, the second factor is transcription factor 1 which will induce cells to produce additional defense proteins and is anti-inflammatory (De Maio & Hightower, 2020).

The results of research from Petrikov (2020), stated that HBOT is an effective treatment because treatment with HBOT has benefits such as inducing an increase in hemoglobin oxygen saturation, a decrease in the intensity of lipid peroxidation, activation of the antioxidant system which is a response to increased ROS, restoration of pro- and antioxidant balance and normalization of apoptosis in patients infected with COVID-19 (Petrikov et al., 2021). Hyperbaric oxygen therapy has a wide range of pressure and time which can be referred to as dosage. The range of HBOT usage is 1.6 to 2.5 ATA. HBOT has anti-inflammatory effects that have been studied at a pressure of 2 ATA for 60 minutes in healthy lungs. Based on the previous explanation, HBOT was administered to COVID-19 patients at a concentration of 2.4 ATA, which is equivalent to 50 minutes of administration. This pressure is equivalent to 2 ATA pressure within 60 minutes. This determination is based on a table used by diving for the maximum dose called Units of pulmonary Toxic Dose (UPTD) or Oxygen Tolerance Unit (OTU). Determination of oxygen therapy in each patient using HBOT aims to avoid toxicity due to prolonged oxygen inhalation (Kjellberg et al., 2020). The results of research from Liang (2020), show that direct administration of HBOT to patients can cause the accumulation of continuous oxygen deficits in tissues and organs throughout the body that experience hypoxia. The occurrence of hypoxia will result in damage to tissues and organs that require optimal oxygen intake so that it is useful to fight viral infections systemically, namely through the bloodstream (Liang et al., 2020).

By increasing circulation and oxygen delivery under high pressure, it will increase tissue uptake, and decrease hypoxia. There is a reciprocal relationship between hypoxia and inflammation, where hypoxic conditions will induce inflammation, on the other hand, inflammation can worsen hypoxia. Controlling hypoxia by administering high-pressure oxygen will suppress inflammation. Based on this fact, HBOT can improve hypoxia in COVID-19 patients, and at the same time has a strong anti-inflammatory effect. Research has demonstrated that hyperbaric oxygen therapy (HBOT) enhances clinical results in COVID-19 patients experiencing low oxygen levels, diminishes the number of patients requiring intensive care unit (ICU) admission, and lessens the necessity for mechanical breathing (Allam et al., 2022; Putri et al., 2023). According to Guo's (2020) research findings, the use of HBOT as a treatment can effectively expedite the recuperation of hypoxemia in patients suffering from COVID-19 pneumonia (Guo et al., 2020). Thibodeux's study conducted in 2020 found that hyperbaric oxygen therapy (HBOT) decreases reliance on mechanical breathing and enhances blood oxygen levels in individuals afflicted with COVID-19 (Thibodeaux et al., 2020).

In a hyperbaric chamber, patients breathe 100% oxygen at a pressure between 1-5 times atmospheric pressure. This will cause the amount of dissolved oxygen in plasma and tissues as the pressure increases. Severe symptoms of COVID-19 disease, including hypoxia and other respiratory problems, can be treated with HBOT. HBOT therapy leads to an increase in oxygen saturation, which can also increase the presence of free radicals. When present in appropriate proportions, these free radicals can help lower proinflammatory cytokines like IL-6, which are responsible for causing cytokine storms (Kjellberg et al., 2020). This is relevant to the research of Zhang (2020), Hadanny (2022), and Cannellotto (2022). COVID-19 patients initially had poor oxygen saturation, and HBOT increased to > 93% (Cannellotto et al., 2022; Hadanny et al., 2021; Zhang et al., 2020).

According to the literature, HBOT has many benefits, but if given at an inappropriate dose, it can lead to oxygen toxicity or complications. Complications that can occur in patients receiving HBOT are tracheobronchitis (cough, substernal burning, and dyspnea on exertion). Neurological complications, such as tunnel vision, tinnitus, nausea, muscle fasciculations, dizziness, and tonic-clonic seizures. Other complications in ophthalmology are retinopathy of prematurity (ROP) in neonates, which can result in permanent blindness, cataracts, and transient myopic changes (Sadri & Cooper, 2024). The administration of HBOT can cause many complications, but none of the 12 articles reviewed by the researcher experienced complications of HBOT.

CONCLUSION

HBOT is an adjuvant therapy for COVID-19 patients. HBOT increases oxygen in the patient's body so oxygen can travel faster to tissues and cells. This increase in oxygen will trigger an increase in ROS, the non-excessive amount of which is beneficial for the body.

The increase in ROS after being induced by HBOT will decrease NF-kB, a protein complex that induces the release of proinflammatory cytokines. Uncontrolled high levels of proinflammatory cytokines cause a reaction in the body, commonly called a cytokine storm. Symptoms caused by increased cytokine storm in patients infected with COVID-19 include high fever and ARDS.

The decrease in NF-kB is caused by increased production of heat shock protein 70 or HSP-70 induced by increased ROS such as hydrogen peroxide (H2O2) after hyperbaric oxygen therapy. HSP-70 will inhibit NF-kB to inhibit the release of proinflammatory cytokines. Thus, providing HBOT therapy in COVID-19 patients as supportive therapy can prevent or accelerate the occurrence of cytokine storms.

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Authors' Contribution

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Conflict of Interest

The authors affirm that the research was conducted free from any commercial or financial affiliations that could be considered a possible conflict of interest.

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