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Background

SARS-CoV-2, which causes coronavirus disease 2019 (COVID-19), was first discovered in December 2019 in Wuhan, China when adults began presenting with severe pneumonia of an unknown cause.[1] SARS-CoV-2 can cause a wide range of clinical manifestations. Individuals can be asymptomatic, but may also experience acute respiratory distress syndrome and multi-organ dysfunction. Common symptoms include fever, cough, sore throat, headache, fatigue, myalgia, and breathlessness.[2] SARS-CoV-2 can penetrate the olfactory mucosa and may enter the brain through the cribriform plate along the olfactory tract, through vagal or trigeminal pathways, or pass through the blood-brain barrier. Once inside the brain, levels of inflammatory cytokines are increased and can lead to altered learning, memory, neuroplasticity, hallucinations, nightmares, cognitive and attention deficits, new-onset anxiety and depression, and psychosis.[3] It has been hypothesized that microglia within the hypothalamus, interacting with mast cells, are responsible for neuroinflammation and proceeding cognitive impairment associated with long-COVID syndrome associated brain fog.[4] Long-COVID syndrome is characterized by symptoms such as mental fatigue (brain fog), difficulty with multitasking, fatigue, headache, insomnia, irritability, inability to find the right words, memory loss, and weakness.[4] Brain fog, common in chronic fatigue syndrome, has been described as "slow thinking, difficulty focusing, confusion, lack of concentration, forgetfulness, or haziness in thought processes."[5] A theoretical treatment for long COVID syndrome, whole body cryotherapy, involves exposing the entire body, including the head, to ultra-low temperatures for a brief time using an enclosed space referred to as a whole-body cryochamber.[6] Theories of cryotherapy leading to neuroprotection include decreased neural cell metabolism, which in turn leads to decreased oxygen consumption, glucose consumption, and cerebral blood flow.[7-9]

Purpose

To evaluate the efficacy of whole body cryotherapy on long COVID syndrome and its current clinical uses.

Methods

A systematic literature review was performed for articles published between 2006-2021 using PubMed and Scopus, with keywords: "coronavirus OR COVID OR COVID-19 OR long COVID" AND "cryotherapy OR cryostimulation OR whole body cryotherapy OR cryochamber OR low temperature" AND "brain fog OR brain OR central nervous system OR CNS" AND "neuroprotection."

Inclusion Criteria

Types of studies

A variety of different research studies were used while conducting this literature review. Studies used for this literature review included primary research studies, cohort studies, meta-analyses, systematic reviews, randomized controlled trials, longitudinal studies, prospective randomized controlled trials, comparative analyses, and other literature reviews. Journal articles were primarily peer-reviewed.

Types of participants

The focus of this literature review was on adults over 18 who were diagnosed with COVID-19 infection and exhibited symptoms of long COVID syndrome. Journal articles including individuals of both genders, all races, and all ethnicities were evaluated.

Types of interventions

Limits were not placed on the type of intervention type used by these studies in order to obtain as much relevant and useful data in order to evaluate the risks, downstream consequences, and treatment of long COVID syndrome with whole body cryotherapy.

Types of outcome measures

Studies were reviewed with the outcomes of assessing the possible efficacy of whole body cryotherapy on long COVID syndrome. The impact of whole body cryotherapy on long COVID syndrome was evaluated. The efficacy of whole body cryotherapy for other diseases, including Alzheimer's

Literature Results

Main Findings

Cryotherapy Procedure

- Cryochambers may use an air compressor that separates nitrogen from oxygen, allowing it to sufficiently cool before re-mixing it with the oxygen and ejecting this vapor into the chamber.[10]
- The other type of cryochamber technology circulates cold nitrogen throughout the walls of the cryochamber to create a low temperature environment.[10,11]
- Cryochambers commonly consist of 2 – 3 chambers, the initial chamber(s) at -60 degrees Celsius (or if two initial chambers, at -10 and -60 degrees Celsius respectively) and one main chamber with temperatures ranging from -110 degrees Celsius to -160 degrees Celsius.[13, 14] Patients will enter the first one (or two) chambers to briefly acclimate (around 30 seconds) and then will proceed to the main chamber where the duration of treatment ranges from 1 to 4 minutes.[10,11]

Clinical Uses for Cryotherapy

- *Anxiety and depression:* In the literature, WBC at temperatures between -60 degrees Celsius and -110 degrees Celsius has been shown to be a valuable treatment when used in supplement to other mental health interventions such as pharmacotherapy and cognitive behavioral therapy.[12]
- *Fibromyalgia:* Patients with fibromyalgia who received 15 whole body cryotherapy sessions found that those who received whole body cryotherapy, from -60 degrees Celsius to -140 degrees Celsius, had a reduced pain score according to the Visual Analogue Scale.[13]
- *Rheumatoid arthritis:* Studies have shown that morning stiffness and pain intensity via the Visual Analog Scale were decreased in patients with rheumatoid arthritis. Treatment with whole body cryotherapy in patients with rheumatoid arthritis also decreased C-reactive protein and inflammatory cytokines interleukin-6 and tumor necrosis factor-alpha.[14,15]
- *Multiple sclerosis:* One study found that patients with MS who received WBC between the ranges of -110 degrees Celsius and -160 degrees Celsius saw an improvement in depressive status and functional status[16]

Cryotherapy Mechanism of Neuroprotection

- Underlying mechanism currently unknown
- Therapeutic hypothermia has also been shown to decrease lactate production, excitotoxins, and decreased ischemia through the downregulation of CaSR (calcium-sensing receptor) induced GABA release.[17]
- Theories of cryotherapy leading to neuroprotection include decreased neural cell metabolism, which in turn leads to decreased oxygen consumption, glucose consumption, and cerebral blood flow.[7-9]
- Another theory on the neuroprotective mechanisms of therapeutic hypothermia is activation of cold-induced RNA binding protein (CIRBP). CIRBP helps protect against oxidative stress on neural cells and subsequent apoptosis.[18]
- cryotherapy can assist in maintaining the integrity of the blood brain barrier through the reduction of matrix metalloproteinases.[18]

Cryotherapy Usage in long COVID syndrome

- Currently, the pathogenesis of brain fog associated with COVID is not well understood, but it is hypothesized that neuroinflammation plays a key role.[19]
- Patients with severe COVID symptoms have been shown to have decreased cerebral blood flow and increased inflammatory cytokines which have been linked to hypoxic injury to the brain.[20]
- Malondialdehyde, an antioxidant marker that rises with total antioxidant capacity, has been shown to significantly decrease in patients affected by COVID-19.[21]
- A study involved exposing rats to whole-body cryotherapy and seeing the effects on their antioxidant levels found that malondialdehyde levels were elevated in rats exposed to -60°C temperatures for one minute, however these values were not statistically significant. When the total antioxidant capacity of the rats exposed to cryotherapy was compared with controls, the rats exposed to cryotherapy had a statistically significant increase in total antioxidant levels.[22]
- Cryotherapy targeted to the cephalic region could offer a feasible method to relieve some symptoms associated with brain fog associated with long COVID.
- Although the pathophysiology of brain fog associated with COVID-19 has not been fully understood yet, cryotherapy has been shown to modulate many inflammatory processes that coincide with COVID-19.

Efficacy of Cryotherapy

- Several theories have explained the mechanism of whole body cryotherapy as providing neuroprotection against oxidative stress on neuronal cells and decreasing the proinflammatory cytokines[1,23]
- A pilot controlled study involving 45 COVID patients with anosmia were assessed using a visual analogue scale (VAS) to evaluate the level of olfactory deficit before, after, and weeks after whole body cryotherapy. The participants in the high dose whole body cryotherapy group reported a higher VAS score after the treatment compared to the low dose whole body cryotherapy group and the control group that received no intervention.[24]

Future Directions

- Cryotherapy is not currently approved by the Food and Drug Administration.
- The current literature theoretically suggests that whole body cryotherapy may be beneficial as a treatment for long COVID syndrome.
- Further literature review on the neuroprotective mechanisms of whole body cryotherapy will need to be conducted
- Randomized control clinical research trials should be conducted to evaluate the efficacy and possible long-term consequences

Conclusion

Whole body cryotherapy has various medical uses and is used mostly in patients suffering from inflammatory diseases, skin lesions, and neurocognitive diseases. Whole body cryotherapy has been used in post COVID patients with anosmia, which indicates promising future research in patients with COVID induced brain fog patients. Although whole body cryotherapy might be safe and beneficial for patients with COVID induced olfactory dysfunction, further research is needed to confirm the findings of this pilot study and to understand the mechanism of whole body cryotherapy in patients with anosmia.[24] Additionally, a limitation to this study is that it heavily relied on self-reported assessments with no blinding procedure.[24] Despite the many uses of cryotherapy, more research needs to be conducted to assess the effectiveness of cryotherapy in long COVID syndrome patients and if there are any consequences in doing WBC. The exact mechanism of COVID related brain fog is not well understood, but several theories have explained the possible pathological mechanism behind brain fog such as neural inflammation affecting the level of neurotransmitters in the body. These circulating neurotransmitters such as serotonin, may explain some of the associated symptoms of brain fog. Understanding the underlying mechanism of COVID related brain fog may give better insight on how to treat the condition. Furthermore, the research may help find ways to prevent the complication of brain fog from arising. Further research will need to be done in order to fully assess the efficacy and safety of whole body cryotherapy for long COVID syndrome.

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