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Research article

The Development of Pulmonary Rehabilitation Protocol for Long Covid Patients

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Abstract

Patients with long COVID report various levels of respiratory discomfort, chest pain, and anxiety. This paper reported on a retrospectively collected data and therapeutic protocol that was created based on empirical experience with long COVID patients. Laser and high-intensity electromagnetic stimulation therapies were used in 30 patients (n=14 men; n=16 women; average age 49 ±14.8 years). Statistically significant difference ($p<0.05$) was observed in decrease of chest pain, score of Hamilton Anxiety Rating Scale, and increased levels of oxygen saturation. The combination of laser therapy with high-intensity electromagnetic stimulation seems promising in the treatment of chest pain and anxiety symptoms in long COVID patients.

Keywords: Long COVID; Pulmonary rehabilitation; Laser therapy; Electromagnetic stimulation; TMS

Introduction

By the end of 2019, China reported the emergence of an unknown pathogen causing pneumonia-like symptoms in the infected cases in Wuhan, Hubei. Subsequently, Chinese Center for Disease Control and Prevention detected the origin as a novel virus from the Coronaviridae family. The World Health Organization (WHO) soon confirmed that human to human transmission of the virus has led to a worldwide "pandemic". The virus was named "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) causing Coronavirus disease 2019 (COVID-19). Coronaviridae is a large family of enveloped, positive-sense, single-stranded RNA viruses. Based on the genome structure and phylogenetic relationships, this family is further categorized into four groups; Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus. Alpha and Beta Coronaviruses are specific to mammals and cause respiratory diseases in humans, namely Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome coronavirus (MERS-CoV). Delta and Gamma Coronaviruses cause infection in both mammals and birds. Genetic analysis revealed that SARS-CoV-2 is most probably in the Betacoronavirus category. Infected patients showed different symptoms based on the severity of the disease. In asymptomatic and non-severe symptomatic cases, the host immune system can successfully eliminate the virus and its effects. In severe cases, however, immune system impairment causes cytokine release syndrome which eventually leads to acute respiratory distress syndrome (ARDS). Overall COVID-19-related rates of mortality are low; deaths usually occur in patients older than 60 and those suffering from serious chronic diseases [22].

Long COVID

Most of the patients recover within one or two weeks. However, in approximately 5–10 % of the patients some of the symptoms persist for weeks and months and develop post-COVID syndrome known in literature as "long COVID". According to the CDC [26], long COVID is a set of symptoms that persist or develop 12 or more weeks after the onset of COVID-19 disease that cannot be explained by another cause. Although the majority of patients who have experienced COVID-19 do not have any long-term consequences, there is still a significant number of patients with long-term consequences that manifest at different levels of the cardiopulmonary system and other organs. Patients with long COVID report fatigue, respiratory difficulties (shortness of breath or perception of unspecified respiratory discomfort), cough, pain on the chest, malaise, tingling of the limbs, disorders in digestion, anxiety and depression [22,26].

Rehabilitation of long COVID patients

Many patients experience a variety of problems with normal functioning and require rehabilitation services to overcome these problems. These include a simple screening process; use of a multidisciplinary expert team; four evidence-based classes of intervention (exercise, practice, psychosocial support, and education particularly about self-management); and a range of tailored interventions for other problems [24,25]. As part of a comprehensive solution attending physicians indicate long COVID patients to outpatient pulmonary rehabilitation, which most often includes education, motion therapy, respiratory physiotherapy techniques and other physiotherapeutic procedures, which are chosen according to the patient's difficulties. Conventional techniques are often combined with modern physical modalities. According to the latest available scientific

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literature [17-19], the most frequently used physical modalities in patients with long COVID are lasers [4,9,14,17,18,21,23] and high-intensity electromagnetic stimulation including peripheral and central applications [1,2,12,10-13,19,20].

Laser therapy

Laser therapy is a physical modality which uses laser light radiation for biostimulation and pain relief [3]. The popularity of the application of laser therapies is increasing due to lasers being a non-invasive, painless modality that can be easily administered [3,4]. In recent years, laser therapy has shown promising results in reducing acute pulmonary inflammation [4,9]. Anti-inflammatory and regenerative effects of laser therapy have been observed in the treatment of allergic lung inflammation, vocal fold injuries, periodontitis, and oral lesions [21]. Several studies have reported the positive effects of PBM on lung inflammatory diseases in animal models [14]. Other experimental and clinical investigations also reported the positive effects of laser therapy on acute and chronic pulmonary inflammation [4], and acute pulmonary inflammation induced by intestinal ischemic-reperfusion. Also, it has been observed that laser therapy may be useful for decreasing pulmonary fibrosis. Recently, it has been reported that laser therapy can be used in the acute phase of COVID-19 [3,4,9,14,17,18,23].

High-intensity electromagnetic stimulation therapy

The use of high-intensity electromagnetic fields stimulation is a known method used in neurology and rehabilitation medicine [1,2]. The therapy principle is based on the interaction of electromagnetic fields that pass non-invasively through the human body and induce electric currents. High-Intensity Electromagnetic Field Stimulation (HIEFS) triggers an action potential process in motoneuron and results in muscle contractions. HIEFS can be applied over the muscle and this method is known as peripheral application [5-8]. HIEFS covers multiple therapeutic effects ranging from pain relief to muscle strengthening, increased blood flow in affected tissues and improved ventilation parameters [10-13,15-16]. Recently, it has been shown that this method improves ventilation parameters in patients with long COVID. Silantyeva (2020) reported encouraging results on almost 30% improvement in forced vital capacity and almost 40% improvement in forced expiratory volumes after 15 sessions that were applied every day in long COVID patients. The justification was explained through the effect of enhanced blood enhancement in the thoracic area and myostimulation effect on respiratory muscles. Apart from aforementioned effects, electromagnetic fields can stimulate local circulation and increase oxygenation [15]. Mert et al. (2020) showed in animal studies that Pulsed Magnetic Fields (PMF) even with very low intensity of 1 mT can induce pain relief, antiedematous and anti-inflammatory effects. Study from Ross et al. (2013) revealed that cells continuously exposed to a pulsed electromagnetic field at frequency of 5 Hz demonstrated significant changes in the downregulation of TNF-α and NFkB and also showed a trend in the down regulation of A20. Additionally, the same method can be applied centrally directly over the brain and is known as transcranial magnetic stimulation (TMS). TMS is a noninvasive technique for stimulating the cerebral cortex and altering cortical and subcortical function. Meta-analyses of numerous sham-controlled studies have shown TMS to produce statistically significant antidepressant effects [1,2,5-8,10-13,15-16].

Aim of the study

In this paper we report on a retrospectively collected data and therapeutic protocol that was created based on our empirical experience with long COVID patients, and existing literature that captures the latest pulmonary rehabilitation trends in COVID patients. Knowing that patients with long COVID complain about breathing difficulties and chest pain due to lung inflammation caused by COVID-19, we aimed to develop a therapeutic protocol that would address the most common consequences of COVID-19. Considering that the combination of peripheral application of HIEFS and laser therapy enhance local blood circulation and induce anti-inflammatory effect, we aimed to eliminate chest pain and improve in an indirect way ventilation parameters through increased oxygen saturation, and elimination of consequences of lung inflammation. Additionally, we aimed to decrease the symptoms of anxiety by using TMS. To the best of the author's knowledge, this is the first paper reporting on such a therapeutic protocol in long COVID patients.

Methods

Patients

This paper reports on retrospective analysis of the short-term data which were collected during medical pre-post intervention examinations of 30 long COVID patients that were treated in our medical facility E-Sport Medicine in Tijuana, Mexico during COVID pandemics in 2020.

Inclusion and exclusion criteria

The main inclusion criteria were adult age (18+ years), positive PCR confirming the presence of COVID-19, breathing discomfort and chest pain. We excluded patients with the presence of metal implants; cardiac pacemaker or other inner electronic devices; increased body temperature >37.5°C; negative dynamics of computed tomography data and/or inflammation markers; negative dynamics of electrocardiograms during the previous 2 weeks; high cardiac risks; thrombosis or blood coagulation disorders requiring additional therapy; and general contraindications for pulmonary rehabilitation.

Ethical considerations

The retrospective data collection was in accordance with the principles of Good Clinical Practice (GCP) and applicable national regulations, respecting the rights, safety and well-being of patients who were protected by the ethical principles set forth in the Helsinki Declaration. All patients underwent treatments voluntarily and signed a written informed consent as well as declaration that they are free of contraindications.

Therapy protocol

30 patients were incorporated in a long COVID rehabilitation program in E-Sport Medicine in Tijuana, Mexico. The rehabilitation program consisted of 10 visits to our medical facility that were scheduled three times per week. In total, patients received three laser therapy applications, three HIEFS applications, and four TMS applications.The therapy protocol is described in Table 1.

Therapy apparatus

Laser therapy

A semi conductive Class IV Laser with a Scanning System applicator (BTL Industries Ltd., United Kingdom) consisting of a maximal power of 30 W and 1064 nm wavelength was used. Therapy was applied over the anterior and dorsal side of the trunk in the area between 1-6th rib. The preset protocol using a combination of pulsed and continuous laser emission modes was used. The power was adjusted based on patients´ thermic tolerance yet within the range of comfortable heat perception.

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Table 1: Long COVID rehabilitation program from E-Sport Medicine in Tijuana, Mexico. The detailed description of individual therapies that were delivered to long COVID patients. Legend: High-intensity electromagnetic field stimulation (HIEFS); Transcranial Magnetic Stimulation (TMS)

Day of visit	Applied therapy
1	Laser therapy
2	Laser therapy
3	Laser therapy
4	HIEFS
5	HIEFS
6	HIEFS
7	TMS
8	TMS
9	TMS
10	TMS

Figure 1: Application of laser therapy with the Scanning System.
(Courtesy of: E-Sport Medicine in Tijuana, Mexico)

Figure 2: BTL-6000 High Intensity Laser with the Scanning System applicator.
(Courtesy of: BTL, source www.btlnet.com)

Figure 3: BTL-6000 Super Inductive System.
(Courtesy of: BTL, source www.btlnet.com)

Figure 4: Application of TMS (Courtesy of: E-Sport Medicine in Tijuana, Mexico).

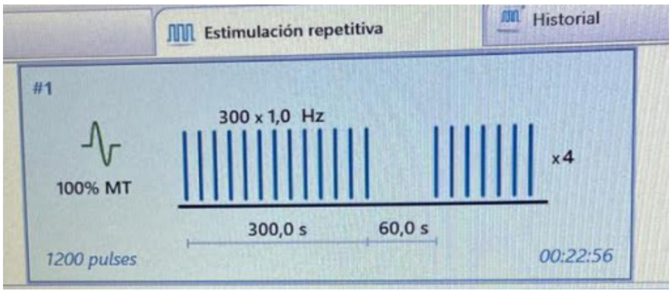

Figure 5: Therapy parameters of TMS (Courtesy of: E-Sport Medicine in Tijuana, Mexico).

HIEFS

Patients were treated with the BTL-6000 Super Inductive System (BTL Industries Ltd., United Kingdom). Therapy was applied on the dorsal side of the trunk. We used the preset protocol that was based on the principle of neuromodulation and increased blood circulation. The intensity of the therapy was adjusted above patients´ sensitive yet below motor threshold within the range of patients´ comfort.

TMS

Patients were treated with the Neuro-MS/D (Neurosoft Ltd., Russia). A 23-minute protocol was used to deliver 1200 pulses to the supplementary motor area (SMA). Frequency of 1 Hz was used in a 5-minute burst mode to trigger trains of pulses followed by a 1-minute pause.

Evaluation methods

Visual Analogue Scale (VAS)

A Visual Analogue Scale (VAS) was used to measure the subjective perception of pain intensity. The scale consists of a 10 cm line divided into 10 equal sections, with 0 representing "no pain" and 10 representing "unbearable pain." Each participant was asked to indicate on the scale the level of chest pain at before the initial intervention (baseline) and after the last therapy.

Hamilton Anxiety Rating Scale (HAM-A)

The Hamilton Anxiety Rating Scale (HAM-A) is the most widely used clinician-administered assessment scale. Each participant was asked to fill HAM-A before the initial intervention (baseline) and after the last therapy.

Oximeter values

Pulse oximetry is a noninvasive and painless method that measures oxygen saturation level in the blood. Level of oxygen saturation was measured at the beginning and at the end of every therapy session. Conventional commercially available pulse oximeter was used.

Data processing and statistical analysis

The Shapiro-Wilk normality test was performed to determine the data distribution in order to verify which statistical test should be used. The negative result of the Shapiro-Wilk test and low number of patients lead to the use of a non-parametric test. VAS, HAM-A scores, and oximeter values that were recorded at the baseline and after the last intervention were calculated as median values. Subsequently, a non-parametric Wilcoxon sign rank test was used to compare patients´ condition before-after the intervention at the significance level $p<0.05$.

Results

We collected data from 30 patients (n=14 men; n=16 women; average age 49 ±14.8 years). None of the patients reported any side effects or problems following any of the treatments. Statistically significant difference ($p<0.05$) was observed in VAS, HAM-A and levels of oxygen saturation. Chest pain evaluated by VAS decreased from 7.6 to 1.1. (Figure 6). HDRS scores decreased from 24.96 to 2.4 (Figure 7). The median value of oxygen saturation increased from 95% to 98% SpO2 (Figure 8).

Discussion

This paper reports on management of respiratory difficulties, chest pain and anxiety in long COVID patients by using laser therapy and HIEFS modalities.

In this study a Class IV laser with a 1064 nm wavelength and 30W maximal power output was used. The major advantage of Class IV laser therapy is its high power and wavelengths above 1000 nm which penetrate deeper into joints, muscles and organs. A 1064 nm wavelength has the ability to penetrate into deeper tissues and reduce pain and inflammation in deeper areas such as lungs [3-4]. The use of a maximal power output of 30W was used based on two major factors. High power output allows for the application of a thermic effect to the treated area which is helpful for chronic patients such as in case of long COVID condition. Furthermore, the higher the power the more energy can be delivered to the treatment area in a shorter time span. This is beneficial for both the therapist and patient as the

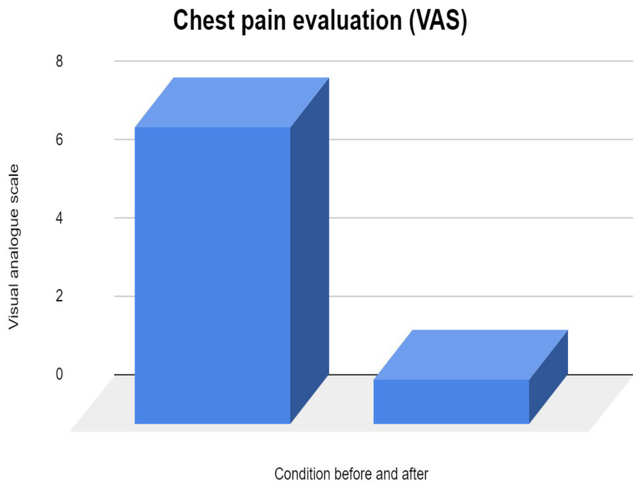

Figure 6: Chest pain evaluation with VAS. Comparison of baseline and post-intervention values showed a decrease from 7.6 to 1.1. Legend: Visual Analog Scale (VAS).

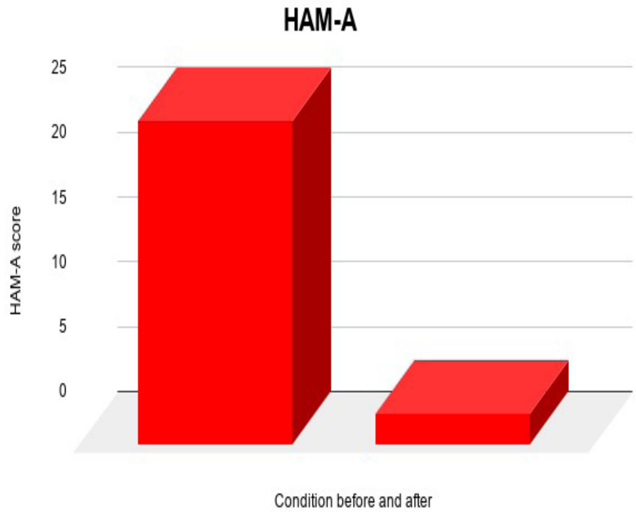

Figure 7: Anxiety evaluation with HAM-A. Comparison of baseline and post-intervention values showed a decrease from 24.96 to 2.4. Legend: Hamilton Anxiety Rating Scale (HAM-A).

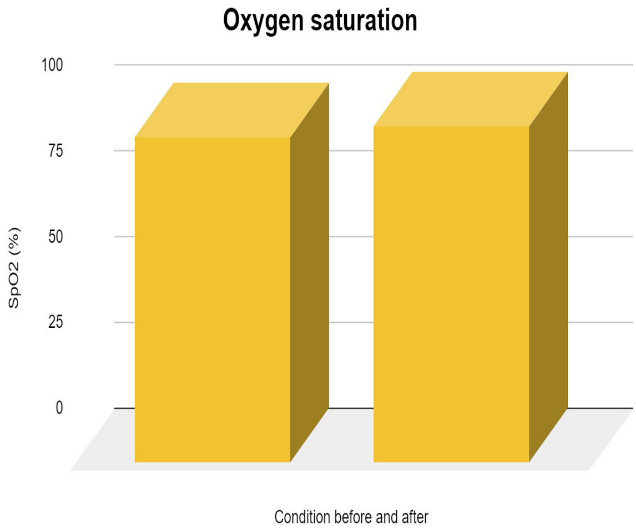

Figure 8: Oxygen saturation measured by pulsed oximeter. Comparison of baseline and post-intervention values showed a decrease from 95% to 98% SpO2.

time of the therapy is reduced to deliver a specific dose of laser energy when compared to a lower powered device which will have a longer duration to deliver the same amount of energy. Both of these arguments show that power output and wavelength are important factors in laser therapies. Despite different parameters, the underlying principles of laser therapy remain the same as in previously published studies [9,14,17-18,23]. Anti-inflammatory effects of laser therapy are based on altering prostaglandin synthesis, decreasing interleukin 1, enhancing lymphocyte response, and decreasing C-reactive protein and neopterin levels. Furthermore, laser therapy can reduce pain by altering the release of chemical mediators such as histamine and bradykinin [17-18]. Our results provide evidence that treatment with this Class IV laser had a significant effect on decreasing the VAS score of chest pain in long COVID patients. This further supports the notion that Class IV laser, in accordance with these parameters of 1064 nm and 30 W powers, could be an important modality for treating long COVID patients due to a significant reduction in pain. It is important to note that although the VAS scale is a subjective tool in assessing pain, it is commonly used due to its availability and ease to administer [3-4,9,14,17-18,23].

It has been previously shown that pulsed electromagnetic fields stimulate local circulation and increase oxygenation in the treated area. Mert et al. (2020) showed in animal study that pulsed magnetic fields (PMF) even with very low intensity of 1 mT can induce pain relief, antiedematous and anti-inflammatory effects. Study from Ross et al. (2013) revealed that cells continuously exposed to a pulsed electromagnetic field at frequency of 5 Hz demonstrated significant changes in the downregulation of TNF-α and NFkB and also showed a trend in the down regulation of A20. In this study a device with a high-intensity electromagnetic field of 2.5 Tesla was used. The main advantage of powerful devices are extended options to treat various conditions and also depth of penetration of electromagnetic energy to deep-lying tissues. Furthermore, HIEFS is also known for improving ventilation parameters by stimulating the respiratory muscles in neurologic patients [10-12]. Additionally, HIEFS has been shown as an important modality in conditioning weakened respiratory muscles in patients with severe COVID-19 pneumonia thanks to myostimulation effect [19]. Our findings further confirm the available data that HIEFS can be used as an effective tool for management of respiratory symptoms in long COVID patients due to its inflammatory and myostimulative effects which are thought to contribute to increase of oxygen saturation.

Infection-triggered perturbation of the immune system could induce psychopathological conditions in patients with COVID-19. According to the latest research, a significant number of patients reported depression, anxiety, and insomnia. It has been also shown that females suffered more for both anxiety and depression. There is an extensive number of studies that have investigated the efficacy and safety of TMS [1-2,5-8]. Generally, this therapy is safe and very well-tolerated by the vast majority of patients. To the best of the author's knowledge, this is the first study that reports on use of TMS in long COVID patients. Our findings further support the notion that TMS is an effective treatment for anxiety.

Conclusion

The combination of laser therapy and HIEFS seems promising in the treatment of long COVID consequences. We are aware of limitations such as the small sample size and lack of long-term follow-up data. For that, we do not overemphasize and generalize the results to a wider spectrum of long COVID patients population. However, our findings provide a foundation for possible future clinical study as all three modalities should be investigated over longer periods in different populations to further determine its effectiveness in long COVID patients.

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