



Effects of low laser level therapy in rehabilitation of patients with COVID19 pneumonia

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Abstract

Introduction. An unprecedented public health crisis has been triggered worldwide by SARS-CoV-2's high contagiousity and its mortality rates of 1-5%. Although the majority of COVID-19 cases have a good outcome, there is a small percentage that develop severe pneumonia and cytokine storm and may be in the need of mechanical ventilation.

Methods. Identifying the exact drivers of the excessive inflammation and the biomarkers that can predict a hyperinflammatory response to SARS-CoV-2 would be extremely helpful in finding efficient anti-inflammatory interventions that may stop the progression to acute respiratory distress syndrome (ARDS).

Results. In the search for such interventions we have identified the promising effect of low level LASER therapy (LLLT) on lung inflammation from COVID-19 pneumonia. Due to its well known anti-inflammatory effect and modulatory activity on immune cells, laser therapy may be able to decrease lung and systemic inflammation without affecting lung function in acute lung lesions, relieve respiratory symptoms, normalize respiratory function and stimulate the healing process of lung tissue. The recovery time may also be significantly shortened and all blood, immunological and radiological parameters may improve.

Conclusions. This findings need further confirmation from clinical trials but we are hopeful for their contribution on the global battle against COVID-19 pandemic.

Keywords: SARS-CoV-2, pneumonia, low LASER level therapy, anti-inflammatory effect, cytokine storm,

INTRODUCTION

SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) belongs to the betacoronaviruses group, line 2, Sarbecovirus subgenus. Coronaviruses are enveloped viruses, of the single-stranded RNA type with positive polarity (+ssRNA), with large dimensions, of about 125 nm (1). SARS-CoV-2 causes a respiratory infection called COVID-19 (Coronavirus infectious disease-2019), with an average incubation period of about 5 days (with limits between 2 to 14 days). The disease is characterized by predominantly respiratory symptoms (fever, cough, difficulty in breathing) of moderate intensity in 80% of cases, but may have severe manifestations (bilateral interstitial pneumonia - the most common complication in coronavirus infection), with progression to respiratory failure, Acute respiratory distress (ARDS) as the leading cause of death (1).

Current data suggest that 80% of cases are asymptomatic or mild; 15% of cases are severe (the disease requires oxygen administration) and 5% are critical, requiring mechanical ventilation and interventions that support

vital functions (2). Patients who have survived this condition may develop - as a complication, a syndrome characterized by physical, mental and cognitive disorders. The "intensive care syndrome" may also develop which, in addition to methods of recovery of the respiratory system, may require complex musculoskeletal rehabilitation (2).

LASER therapy is a non-invasive, atraumatic, aseptic physiotherapy procedure with many applications in the field of medical rehabilitation, from pain therapy to the direct action it has on tissue and biological process stimulation, being an alternative to avoid the renal and hepatic side effects of analgesic and anti-inflammatory medication (3,4). The effects of LASER therapy are photochemical in nature, by absorbing LASER light at the level of photoreceptors, which triggers biological changes at the cellular level and increased intercellular activity, depending on the wavelength. Among the benefits of this therapy we mention: the analgesic, anti-inflammatory, anti-edematous effects, the improvement

of blood and lymphatic circulation, muscle relaxation, acceleration of nerve and bone tissue regeneration, stimulation of immunity, decrease of the healing time of wounds and scars (5).

In SARS-CoV-2 viral pneumonia, low level LASER therapy (LLLT) reduces inflammation without affecting lung function in acute lung lesions, relieves symptoms and stimulates the healing process of lung tissue (6). Other forms of physical therapy, such as low intensity pulsed ultrasound technique, with intensity typically less than 100 mW/cm², with antiinflammatory (7) and antioxidant effects (8) is also proposed now as treatment modality for discrete pulmonary lesions in patients with COVID-19 (9).

Discussion

The physiopathology and mechanism of action of LASER in acute lung inflammation

At the alveolar level, the virus infects type II pneumocytes having an initial stage of viral replication and a second stage of proinflammatory programmed cell death. Some molecular patterns are then released, and recognized by neighbouring epithelial cells, by endothelial cells and by alveolar macrophages. They trigger the inflammatory response by generating proinflammatory chemokines and cytokines such as IL-1 β , IL-6, IL-7, IL-8, IL-10, TNF α , which further attract inflammatory cells such as monocytes, macrophages and lymphocytic T cells. Severe COVID-19 have been associated with elevated inflammatory markers and increased cytokine levels. These markers are prognostic for the requirement of mechanical ventilation, the development of ARDS, and death in COVID-19 (10).

In the case of a dysfunctional response, immune cells continue to accumulate, producing excessive cytokines, which causes an excessive inflammatory response, the so-called cytokine storm. At the pulmonary level, this inflammatory process results in the thickening of the alveolar interstitium with the accumulation of fibrin and the formation of hyaline membranes, with the increase of capillary permeability and the activation of coagulation. All this leads to pulmonary oedema, with massive alveolar destruction, fibrosis, respiratory failure and acute respiratory distress syndrome (11).

The main actions of interleukin 6 (IL-6) on lymphoid and non-lymphoid cells are mechanisms that modulate the body's immune and inflammatory responses. Although many of these functions overlap with those of type 1 interleukin (IL-1), such as the synthesis of acute phase reactants and fever, IL-6 also has anti-inflammatory effects. Similarly IL-1, the most important source of IL-6 is represented by macrophages, being synthesized by T and B lymphocytes, by fibroblasts and by endothelial cells, by keratinocytes, synoviocytes, chondrocytes and epithelial cells. Thus IL-6 is produced in response to bacterial and viral infections, to inflammation or trauma,

quickly reaching detectable plasma levels, unlike many other cytokines(12).

In addition to proinflammatory actions, IL-6 also mediate a number of anti-inflammatory effects, while IL-1 and TNF induce each other's synthesis, as well as that of IL-6, IL-6 completes this inflammatory cascade because it inhibits IL-1 and TNF syntheses (12). IL-8 contributes to the pathophysiology of ARDS, neutrophil chemotaxis and survival in lungs and TNF- α is responsible for the adhesion and activation of neutrophils, the procoagulant effect and oedema. It can also stimulate the release of IL-6 (11,13). Monocyte chemotactic protein (MCP-1) is a chemokine with a crucial role in monocyte recruitment. Its level increases in lung inflammation. Monocyte migration may be reduced after therapy due to decrease in MCP-1 (14).

On the other hand, the role of IL-10 is not clear yet. Some authors have reported it as a predictor of poor prognosis, while others know it as a regulatory cytokine that is released during the cytokine storm. Its role is to limit the immune response to pathogens and to restrict host cell damage. Several studies have stated that an imbalance between TNF α and IL-10 levels increases host cell damage and the risk of complications (15).

Another theory in the physiopathology of COVID-19 pneumonia is the role of decreasing the number of CD4 + and CD8 + T cells and lymphocyte imbalance. T cells play an important role in the immune response against viral pathogens. CD4 + helper T cells guide B cells, and cytotoxic T cells and CD8 + cytotoxic cells eliminate viral pathogens by releasing molecules such as perforin, granzyme, and IFN γ (16).

In acute lung inflammation, LLLT can increase TNF α levels and improve the balance of inflammatory processes. It significantly reduces IL-8 levels, can alleviate ARDS and reduces mortality (16).

Photomodulatory therapy also contributes to healing by promoting apoptosis of inflammatory cells while suppressing apoptotic pathways in lung tissue. In a model of acute lung injury, low-intensity laser therapy reduced DNA fragmentation and apoptotic way activity by increasing B-lymphoma-2 (Bcl-2) cells, the key regulator of the intrinsec or mitochondrial way for apoptosis in alveolar epithelial cells, while promoting DNA fragmentation in inflammatory cells (17).

In pulmonary idiopathic fibrosis, the laser inhibits pro-inflammatory cytokines and increases the expression of proliferating cellular nuclear antigen, it attenuates airway remodelling by balancing proinflammatory and anti-inflammatory cytokines in lung tissue, and inhibiting fibroblast secretion of pro-fibrotic cytokines. It offers synergy in combination with medical treatment. It has a synergistic anti-inflammatory action on alveolar macrophages associated with N-acetyl cysteine, effective against cough and lung diseases (18).

Photomodulatory therapy is proving to be able to enlarge CD + and CD8 + cells and improve the balance between them. While this therapy has been widely used to improve healing, potential negative results have also been observed. Laser therapy could induce fibroblastic migration which, in turn, causes the deposition of collagen in the lung tissues and thus the appearance of pulmonary fibrosis (19).

On the other hand there are studies claiming that photobiomodulatory therapy can have an anti-fibrotic effect by lowering TGFβ in both fibroblast cells and lung tissue (20).

Therapeutic technique and LLLT dosing

The Multiwave locked system (MLS) LASER therapy used in these studies uses a mobile scanner with 2 laser diodes, emitted in pulsed mode at 905 nm and 808 nm, respectively, the two wavelengths of t LASER working simultaneously and being synchronized. The scanner is positioned above the lung area at about 20 cm, each lung being scanned from the top to the base (21). The LASER field was focused on the median edge of the scapula, opening the lung fields, thus reducing the thickness of the chest wall to theoretically improve laser penetration into lung tissue (21).

The therapeutic dose used according to calculations performed by Dr. Soheila Mokmeli, co-author of the main study conducted with Dr. Scott Sigman-main investigator and lead author of the first use of LASER therapy in the treatment of a patient with COVID-19 induced pneumonia, was just over 0.01 J/cm² of LASER energy in the lungs. This dose was able to penetrate the chest wall into the lung tissue creating an anti-inflammatory effect that theoretically blocked the effects of the cytokine storm seen in COVID pneumonia (21,22).

Therapeutic protocol for various forms of SARS-CoV2 virus infection

We present below the main parameters of LLLT depending on the severity of COVID-19 infection (Tabel I for mild form of COVID-19, Tabel II for moderate and severe forms of COVID-19).

Laser type	Average power	Dosage	Area	Time required	Sessions
Infrared laser (780-900 nm) or Red light laser (630-660 nm)	50-100 mW	4-6 J/cm ²	10 cm ²	1-2 minutes/cm ²	3-8 sessions once/day

Table I. Therapeutic protocol: COVID-19 mild form

Laser type	Average power	Dosage	Area	Time required	Sessions
Infrared laser (780-900 nm) or Red light laser (630-660 nm)	50-100 mW	6-10 J/cm ²	10 cm ²	2-3 minutes/cm ²	3-10 sessions once/day

Table II. Therapeutic protocol: COVID-19 moderate – severe forms (23)

Clinical trials have shown that the laser used in COVID-19 pneumonia has reduced respiratory symptoms by normalizing respiratory function; the recovery time has been significantly shortened and all blood, immunological and radiological parameters have improved (24).

We mention the post-treatment results for the patients in the first randomized pilot study that involved patients with confirmed COVID-19, conducted in August 2020 by Dr. Sigman:

1. SaO₂ increased from 93-94% to 97-100%
2. The O₂ requirement decreased from 2-4 L/min to 1L/min
3. The RALE radiographic score improved from 8 to 5
4. Pneumonia severity index improved from class V (142) to class II (67)
5. Pulmonary indices, Brescia-COVID and SMART-COP, both decreased from 4 to 0
6. PCR normalized; from 15.1 mg/dL to 1.23 mg/dL
7. Ferritin decreased from 359 ng/mL to 175 ng/mL
8. Clinical recovery was a total of 3 weeks, while the mean time is usually 6 to 8 weeks.

The results confirm the anti-inflammatory effects described above as evidenced by the reduction in the levels of pro-inflammatory dosed markers, IL-6 and ferritin.

Another strength of the therapy is that the method of scanning of this LASER does not present any risk of contamination, because LASER does not come into direct contact with the patient.

Conclusion

Low LASER level therapy (LLLT) can be added to conventional treatment in patients with COVID-19, at different stages of the disease, due to its anti-inflammatory effect and its ability to reduce the recovery time of patients.

Scientific evidence shows that LLLT attenuates cytokines and inflammatory chemokines in the cytokine storm at several levels. In addition, LLLT promotes apoptosis of inflammatory cells and protects alveolar cells from damage. These findings suggest that LASER therapy is a feasible way to treat ARDS.

Conflict of Interest

The authors declare that they have no conflict of interest.

Author contribution

All authors with equal contribution.

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