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Guest Editorial

Photobiomodulation and Antiviral Photodynamic Therapy as a Possible Novel Approach in COVID-19 Management

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Coronavirus disease, COVID-19, or SARS-CoV-2 pandemic is the biggest event and disease that has challenged all humanity, especially scientists in the recent century. This pandemic has affected our lives in all aspects. Medical sciences and novel technologies have been powerless against this invasion and a lot should be done in all aspects of science to embrace these kinds of situations. COVID-19 is a type of coronavirus that initially spread from the city of Wuhan in China in late 2019, spread through the whole world, involved millions of people, and led to thousands of deaths.[1] Due its huge span and spread, everyone in any field should play a role in the management of this disease.

β-Coronaviruses is an enveloped, nonsegmented, positive-sense single-stranded RNA virus genome belonging to the family Coronaviridae. COVID-19 is a coronavirus such as SARS (civet), MERS (camel), etc.[2] It spreads from bats and pangolin to finally humans. COVID-19 is referred to as a self-limiting infectious disease. Usually, patients have mild symptoms that can be recovered after 1–2 weeks. Cases include asymptomatic infected patients (1.2%), mild to medium cases (80.9%), severe cases (13.8%), critical cases (4.7%), and death (2.3% in all reported cases).

Primary viral replication is presumed to occur in mucosal epithelium of the upper respiratory tract (nasal cavity and pharynx), with further multiplication in lower respiratory tract and gastrointestinal mucosa, giving rise to a mild viremia. A few infections are controlled at this point and remain asymptomatic. Some patients have also exhibited non-respiratory symptoms such as acute liver and heart injury, kidney failure, and diarrhea showing a multiple organ involvement.[3]

Angiotensin Convertase Enzyme 2 (ACE2), which is an enzyme that is located on the surface of these cells and is the main receiver of the spike protein of the virus, is the main entry point of the virus to the cell (ACE2). The spike protein of the virus consists of two parts: S1 & S2; S1 is for primary attachment and S2 for viral infusion. ACE2 is mostly expressed in nasal mucosa, bronchus, lung, heart, esophagus, kidney, stomach, bladder, and ileum, so all of these organs are susceptible to SARS-CoV-2.

The most important complication of this disease is Acute Respiratory Distress Syndrome (ARDS). ARDS is a critical lung condition that prevents enough oxygen from getting to the lungs and the bloodstream, which causes death in most respiratory disorders and acute lung injuries such as human SARS-CoV, MERS-CoV, and SARS-CoV-2 infections. Previously, studies showed a close relationship between genetic susceptibility and inflammatory cytokines and ARDS. ACE2, interleukin-10 (IL-10), tumor necrosis factor, and vascular endothelial growth factor are among the genes associated with the development or outcome of ARDS. Elevated levels of plasma IL-6 and IL-8 are in relation with the outcomes of ARDS, which suggest both a molecular explanation for the severity of ARDS and a possible treatment for ARDS after SARS-CoV-2 infection. It is believed that cellular damage caused by fast viral replication, ACE2 downregulation by the virus, and antibody dependent enhancement (ADE) are responsible for aggressive inflammation caused by SARS-CoV-2. SARS-Cov-2 and SARS use the same entry receptor, ACE2, and thisexplains the resemblance of the same cells being infected by them. Although these cytokines are released initially as a defense response, extreme production of pro-inflammatory cytokines and chemokines (known as the cytokine storm) are initially triggered by the epithelial and endothelial cell death and vascular leakage caused by rapid viral replication, which finally leads to a severe pro-inflammatory condition in critically ill patients. Acute lung injury has been related to loss of pulmonary ACE2 function. Due to its role in the renin-angiotensin system, ACE2 downregulation can enhance inflammation and cause vascular permeability.[3]

Unfortunately, there is no reliable treatment or vaccine for SARS-CoV-2 right now and research centers are working on them. Symptomatic treatments are now recommended. Here are some examples: Chloroquine (an approved malaria and rheumatoid arthritis treatment), Kaletra (an anti-HIV drug consisting of lopinavir and ritonavir), Interferon (SNG001): (an inhaled formulation of a drug called interferon β), Remdesivir (viral replication inhibitor), Tocilizumab (Actemra): (a monoclonal antibody blocking IL-6), and Favipiravir (Avigan): (antiviral drug),[4] a genetically modified type of ACE2, called human recombinant soluble angiotensin-converting enzyme 2 or hrsACE2 (prevents COVID-19 from entering the cells significantly). We can

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conclude that recent treatments are focused on the antiviral, anti-inflammatory, stifling the cytokine storm and increasing tissue oxygenation.[5]

Photobiomodulation (PBM) is a photon therapy based on PBM that uses a light source from lasers, light-emitting diodes, and broadband light, in the visible and near-infrared spectrum. Through this mechanism, different methods such as direct laser therapy are used to target tissue, intravenous or transcutaneous lasers are used to target the bloodstream for systemic effects, and laser therapy is used to target deeper tissues such as the transcranial brain.

It has different effects on cells such as proliferation, adenosine triphosphate (ATP) induction, synthesis of DNA and RNA, and activation of cell signaling cascades such as reactive oxygen species (ROS), nitric oxide (NO) release, which activate cytochrome c oxidase and modify intracellular organelle membrane activity, calcium flux, and expression of stress proteins. It also has general effects such as metabolic effects, analgesic effects, anti-inflammatory effects, and, finally, immunomodulatory effects. It is also helpful in regenerative treatments and enhances cellular power in metabolic diseases, brain traumas, neurological diseases, cardiac diseases, dentistry, physiotherapy, physical medicine, and rehabilitation. Interestingly, there are some studies about lung diseases that suggest that NO inhibits the replication cycle of severe acute respiratory syndrome.[6,7]

As mentioned earlier, the most important method for COVID-19 management is oxygenation and faster rehabilitation of the damaged tissue, antiviral effects, and, finally, reduction or controlling the cytokine storm by reducing inflammatory agents.[8] PBM may be used as an adjuvant therapy or even an alternative therapy in all these mechanisms without side effects and drug interactions.

In this disease, we can use different methods of laser therapy. Two methods that are used are non-invasive and minimally invasive therapy: In non-invasive therapy, a possible way is to radiate the laser directly on the lung tissue from the chest and from the back area.[9] This method, called transthoracic PBM therapy, is similar to the same treatments of the brain, which use infrared lasers, such as 810 or 940–970 nanometer, that can cross the skull tissue.[10] These lung treatments can open a new window to therapists, not only in the treatment of ARDS but also in the treatment of other diseases such as tuberculosis, pneumonias, or influenza.

To target blood indirectly, the transcutaneous techniques in the surface arteries, such as wrist, nasal mucosa, the back area of the knee, or even sublingual tissues, might be helpful where the laser can be irradiated directly to the blood.[11,12] However, by radiating the laser to the tibia (bone marrow), we may be able to promote stem cells of this region to induce and modulate the immune system. We can also modulate the immune system via direct laser therapy of thymus or lymphatic nodules.

On the other hand, by using the intravenous laser method we are likely to benefit directly from the systemic effects of laser therapy. According to existing studies, lasers with different wavelengths, such as green for oxygenation, blue for viral reduction and increased NO, and red for increased ATP, can be beneficial. This method can also improve blood biomarkers and the red cells' oxygenation and may even be helpful in the cellular and hormonal innate and adaptive immune system, with minimal interference with the pharmacological treatment methods that are likely to be found, to achieve a decisive treatment. Of course, we can use a combination of treatments. With these immunological effects, we may control the cytokine storm and prevent further damage by it.

Also, with PBM biological effects on tissue regeneration (especially production of ATP), it could go through the lung tissue and help in its rehabilitation. In spite of the drug side effects in the coronavirus disease, different tissues such as the kidney and liver are also at direct risk of the virus (directly targeted by S2 receptors) and indirect risk by the inflammatory storm. Also, to metabolize various toxic drugs that the patient receives, liver and kidneys are weakened and this method decreases the load of these important tissues while helping the patients by resembling the chemical drugs' effects.[11,12] In this field, even the acupuncture laser method may also be used in different ways that require more evidence. In addition, we could use PBM in immune-suppressed patients as a preventive method to prevent their further exacerbation.

Further, there are some wavelengths that can decrease microorganisms directly, such as blue, ultraviolet, or violet wavelengths. We can increase these effects by possibly combining this method with another method known as antimicrobial photodynamic therapy (aPDT).

Photodynamic therapy is a type of photosensitive compound, such as oxygen, and light reaction. In fact, endocellular or extracellular release of ROS induced by this reaction can lead to apoptosis or cell necrosis with minimal damage to adjacent tissues that are most importantly used in cancer therapy.

aPDT and nanomaterial-based antibacterial photodynamic therapy have been investigated as two novel ways of inhibiting bacterial, viral, and fungal infections as photoactivated disinfectants. There are several advantages to these methods, such as lack of long-term toxicity and gene mutations, the ability to remove microorganisms in a very short time, less damage to adjacent tissues, the access to areas with complex anatomy, low risk of bacteremia especially in immune-suppressed patients, and high repeatability without bacterial and viral resistance.[13]

In different studies, different wavelengths were used with photosensitizers, such as curcumin, methylene blue, vitamin B2 (riboflavin), etc., to target microorganisms especially in the blood tissue. Although the viral load in blood is low, we may be able to reduce it even more with laser therapy and the right amount of photosensitizer.[14] In addition, if we could deliver the photosensitizers to the lungs, we may be able to irradiate the laser to them. Blue wavelength does not have high penetration rates and we cannot use them from outside of the body, so we should enter or at least bring the fiber close to the lung or use intratracheal laser therapy. We may benefit from using an indocyanine green-based photosensitizer that has been used in the blood for diagnostic purposes. If we could get this substance to the lungs' cells, it would possibly be more beneficial than other substances, due to the fact that it is activated by a 810-nm laser with more penetration depth.[15]

In conclusion, COVID-19 disease is very unknown, and scientists in any area must manage the most dramatic challenge of the century, in any way possible. As we move forward, we should synchronize our speed with the progression of this disease, or even progress faster than it, so it does not take more lives in the future while challenging humanity. According to mechanisms mentioned earlier, we are referring to the capabilities of PBM and photodynamic therapy. The best use is a combination of both methods, as mentioned earlier. The present treatments are focused on virus removal, tissue oxygenation, and reduction or inhibition of cytokine storm caused by severe inflammation. With a combination of these two methods, we can achieve these goals with minimal interference with pharmaceutical methods and battle this disease with biophysical agents. Of course, in the future, the use of a different modality of PBM and aPDT can be evolved and, by using monoclonal antibodies we could target lung tissue specifically. It can even be improved by using Nano technology, making new photosensitizers in Nano scales, and pasting them to the target tissues to obtain better results.

To sum up, this Nano particle, which can be called neither live nor non-live, is perhaps a flick or inspiration; proud and intoxicating human knowledge should attain the highest point of growth and excellence and be severely challenged so that a revolution in science is created and it warns the human beings to be prepared for the tougher challenges coming in future. We should help each other out in any field, see each other as one, be holistic, get out of our rooms and aquariums, and take a more holistic look at science so that the ship of life on this beautiful planet continues its tranquil journey to a beautiful horizon, and be prepared to face any kind of natural or unnatural turbulence.

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