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Letter to the Editor

Ozone therapy may be an option for COVID-19 patients

Dear Editor,

The Coronavirus outbreak that started in Wuhan is still ongoing and as of Feb 15, 2021, more than 120 million people worldwide have been affected by the disease. Although there is no clear explanation yet for the treatment, scientists are discussing many treatment methods. Vaccine was produced but there is still debate and confusion about the results of vaccine studies and drug research on the disease continues worldwide. Recently, the appearance of different mutations related to Coronavirus has raised global public concerns, and the vaccine-drug debate has gained momentum again. The high viral load and oxidative stress that occurs in the disease are valuable for the pathogenesis and prognosis of the disease.

Ozone therapy, initially applied in medicine by an empirical approach, has now reached a new level; most of the biological mechanisms of ozone action have been clarified, which refer to antimicrobial and antioxidant effects, immunoregulation and epigenetic modification. There are previous clinical studies in the literature showing that ozone therapy has antiviral and antioxidant properties[1-3].

The effective role of ozone therapy in COVID-19 patients is worth investigating and clinical trials have the potential to offer new treatment options. Ozone is an energy-rich and highly unstable form of oxygen[4]. It has proved to be quite effective against Gram-negative and Gram-positive bacteria, viruses, and fungi[5]. Ozone's action is two-fold but simultaneous; it generates direct molecular-level reactions in the medium in which it is released and indirectly destroys bacteria by the production of free radicals[6]. It is generally accepted that oxidation due to ozone starts the destruction of cell walls and cytoplasmic membranes of microorganisms; after the membrane is damaged, permeability increases, and ozone molecule can easily enter into the cell[7].

Viruses may be susceptible to ozone, but this susceptibility is variable to lipid-coated encapsulated viruses which have been found to be the most sensitive, and coronavirus is one of them. The envelopes of coronaviruses are rich in cysteine, and their residues have to be intact for viral activity. Cysteine contains a thiol or sulfhydryl group (-SH); many viruses, including Coronavirus, need these reduced sulfhydryl groups for cell fusion and entry[8]. Sulfhydryl groups are vulnerable to oxidation and are, therefore, sensitive to ozone due to their oxidizing powers. Peroxides created by the application of ozone oxidize cysteines and show long-term antiviral effects that may serve to further reduce the viral load[9]. Thus, the structural integrity of the virus becomes impaired. Once their capsid is removed, the virions cannot continue or reproduce. Ozone provides unique therapeutic possibilities by disrupting the creation of viruses. Ozone has an immunomodulation function on the immune system through the second messenger activation of various transcription factors in the cytoplasm. These are inducible hypoxia factor type 1 alpha (FHI-Alpha), nuclear factor kappa B (NF-kB), transcription factor Nrf2. These factors will trigger through the release of proteins all the beneficial mechanisms attributed to ozone[10]. Ozone can be a major contributor to the treatment of COVID-19 patients with its ability to induce the release and modulation of interferons and certain cytokines (IL-4, IL-6, IL-10, TNF) that reduce inflammation. Benefiting from the immunomodulatory effect of ozone therapy against cytokine storm in COVID-19 patients can be used as an option or helper to the routine therapy methods.

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In ozone therapy, lower doses lead to placebo effect, and higher doses lead to toxicity[11]. Because of this, accurate adjustment of ozone doses is very important. Moderate oxidative stress activates nuclear factor-erythroid 2-associated factor-2 (Nrf-2). Nrf-2, on the other hand, triggers the transcription of antioxidant response elements (ARE). However, severe oxidative stress, nuclear transcription factor kappa (NFkB) click by activating an inflammatory response and, ultimately, cyclooxygenase (COX)-2, prostaglandin (PG) E2 and leads to tissue damage by increasing the production of cytokines[12]. The key point in ozone therapy is the adjustment of oxidative stress levels.

In systemic ozone applications, reactive oxygen compounds and lipid peroxidation products formed after interaction with plasma trigger different mechanisms in many cells. Activation of the pentose phosphate pathway as a result of erythrocytes encounter with ozone causes the acceleration of glycolysis, an increase in 2,3 diphosphoglycerate values causes a right shift in the oxyhemoglobin curve, which allows easier release of oxygen to hypoxic tissues[7,11]. This condition is critical for the improvement of hypoxia and increased oxygen saturation in COVID-19 patients. Ozone has biological properties that indicate that it may play a possible role in the treatment of SARS-CoV-2 or may be part of the treatment for a particular group of patients. Coronaviruses have rich cysteine in spike-shaped proteins that are characteristic of the viral surface and can be easily damaged by ozone. Rich cysteine residues in viral membrane proteins mediate virus binding and entry into the host cell. This cysteine appears to be functionally important for the production and maintenance of the virus. Coronavirus may become ineffective as a result of denaturation of cysteine-rich spike protein with ozone. Ozone therapy has been shown to be an effective and safe treatment. Ozone, in addition to being the best immunomodulator that exists in the inflammatory response, can damage these cysteine residues. Given the characteristics of the disease, ozone may be an effective treatment option for COVID-19. Applying ozone therapy to the appropriate patient population could reduce mortality and be important for pandemic control. The present paper is to encourage scientific argumentation but the correctness of the theory needs confirmation *via* conduction of appropriate *in vitro* and *in vivo* studies.

Conflict of Interest
The Authors declare that they have no conflict of interests.

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