Ozone therapy as an adjunct in the treatment to COVID-19

Article · May 2020

DOI: 10.33233/rbfe.v19i2.4116

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RBFEx
ISSN: 2675-1372
Brazilian Journal of Exercise Physiology

Editorial

Ozone therapy as an adjunct in the treatment to COVID-19

Ozonioterapia como adjuvante no tratamento da COVID-19

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The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) called "coronavirus 2019" (COVID-19), has become a threat to the general population and health professionals worldwide [1]. The clinical features of COVID-19 is like that of other respiratory viruses, with specifically, fever, generally dry cough, tiredness and, in more severe cases, dyspnea, pulmonary bleeding, severe lymphopenia and renal failure [2].

For diagnosis, the World Health Organization (WHO) recommends the collection of samples from the upper or lower respiratory tract. In the laboratory, the amplification of the genetic material extracted from the saliva or mucus sample is carried out by means of a reverse transcription followed by a polymerase chain reaction (RT-PCR), which involves the synthesis of a double-stranded DNA molecule from of an RNA template, in the search for conserved parts of the coronavirus genetic code. In patients with a confirmed diagnosis, the laboratory test should be repeated to assess the release of viral particles, before leaving the isolation [3].

The clinical manifestation and severity of the disease is directly related to the health condition of the infected individual. Symptoms are often mild as in a common cold or flu and it can progress to pneumonia. Ventilatory support therapy such as oxygen therapy and/or mechanical ventilation is necessary as an intervention method in the most severe cases of the disease [4]. Individuals with chronic respiratory diseases and other comorbidities can present the most severe form of COVID-19 and, for this reason, care with prevention should be emphasized [5].

Although there is no specific recommended antiviral treatment and no vaccine available, several therapeutic approaches have been proposed, such as: lopinavir/ritonavir [6]; chloroquine/hydroxychloroquine [7]; alpha interferon [8]; and remdesivir, an RNA polymerase inhibitor with in vitro activity against several RNA viruses, which have been shown to be effective in preclinical trials in the treatment of coronavirus infections [9].

In this moment of serious global health crisis, we highlight the possibility of using ozone gas or ozone therapy as an adjuvant in the antiviral

Received: April 16, 2020; Accepted April 27, 2020.

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treatment of COVID-19. Ozone gas (O_3) is a molecule that consists of three oxygen atoms in a dynamically unstable structure due to the presence of mesomeric states. The gas is colorless, has a bitter odor and its basic function is to protect humans from the harmful effects of ultraviolet radiation. Ozone is a natural compound that is easily generated in situ from oxygen or air and decomposes into oxygen with a half-life of about 20 minutes [10,11].

Ozone therapy is a technique that uses an oxygen-ozone gas mixture for medicinal purposes. This technique assumes that O_3 dissociates quickly and releases a reactive form of oxygen that can oxidize cells, increasing the availability of oxygen and ATP for cellular activity [11]. Ozone increases the rate of glycolysis of red blood cells, stimulating 2,3-diphosphoglycerate, promoting an increase in the amount of oxygen released to the tissues. Additionally, it activates the Krebs cycle, improving the oxidative carboxylation of pyruvate, stimulating the production of ATP. It also leads to a significant reduction in NADH and helps to oxidize cytochrome C. The production of prostacyclin, a potent vasodilator, is also induced by O_3 [10,12].

Ozone is deemed to be a prodrug, since it induces the activation of a biochemical cascade with multiple systemic antioxidant actions (Figure 1) [10,11]. O_3 reacts with all biomolecules in cell membranes, including lipids, proteins, carbohydrates and DNA [13]. The unsaturated fatty acid, which is found in cell membrane phospholipids, reacts with O_3 to generate hydrogen peroxide (H_2O_2) and 4-hydroxinonenal aldehyde (4-HNE). H_2O_2 promotes the transcription factor Nrf2 pathway and protein synthesis, which favor cell survival. Degradation of 4-HNE sends a signal of transient oxidative stress, activating the synthesis of various substances that respond to cellular oxidative stress such as: y-glutamyl transpeptidase, heat shock protein 70 (HSP-70), hemoglobin oxygenase-1 (HO -1); in addition to antioxidant enzymes, such as superoxide dismutase, glutathione peroxidase, catalase and glucose-6-phosphate dehydrogenase (G6PDH). This process represents the basis of the paradoxical phenomenon, for which an oxidizing molecule, such as O_3, triggers a potent antioxidant reaction [11-13].

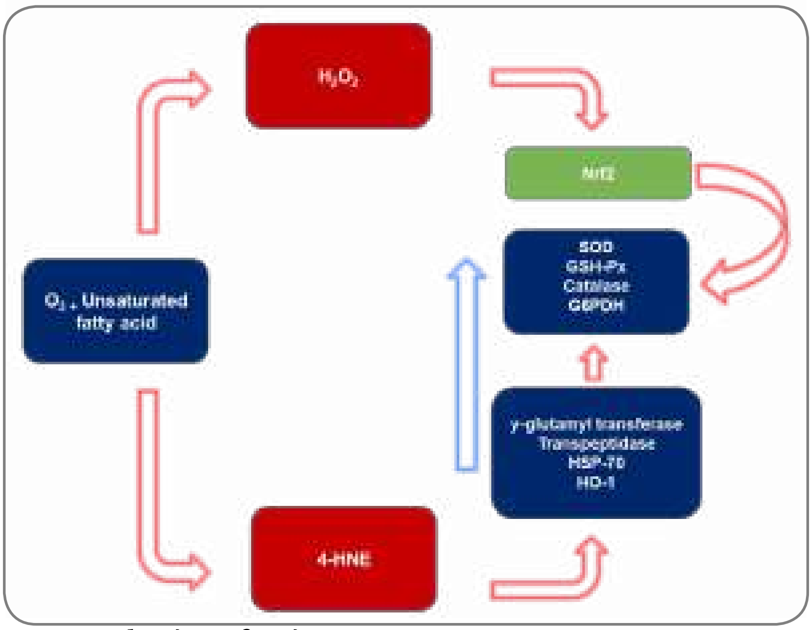

Figure 1. The ozone mechanism of action.
Source adapted from Sciorsci *et al.* [11]. O_3 - Ozone; H_2O_2 - hydrogen peroxide; 4-HNE - 4-hydroxynonenal; Nrf2 - erythroid nuclear factor 2 related to factor 2; SOD - superoxide dismutase; GSH-Px - glutathione peroxidase; G6PDH - glucose-6-phosphate dehydrogenase; HSP-70 - heat shock protein 70; HO-1 -hemoglobin oxygenase 1.

The use of ozone has been shown to inactivate different microorganisms, such as bacteria, fungi and different viral strains, including the coronavirus [14]. Coronavirus is an enveloped RNA virus where glycoproteins rich in cysteine present in the viral envelope assist in recognition by host cells [3]. Cysteine contains a reduced thiol or sulfhydryl (-SH) group, essential for fusion and entry of the virus into the cell. Sulfhydryl groups are vulnerable to oxidation and, therefore, susceptible to ozone, due to their oxidizing power. Peroxides created by ozone administration oxidize cysteines and show antiviral effects that can serve to reduce viral load [15,16].

The immunological action of ozone is fundamentally directed on monocytes and T lymphocytes, which, once induced, release small amounts of cytokines, such as: interferon-gamma (IFN-y) tumor necrosis factor (TNF) and interleukin-2 (IL-2). The modulating activity of inflammation and the improvement of oxygenation in tissues, in combination with the induction of the activation of antibodies and cytokines, help to structure the immune response to fight several viral types [10,16].

Thus, ozone therapy may be potentially useful for SARS-CoV-2 infection in two therapeutic categories: surface disinfection [14]; or in systemic use as an additional compound, in order to improve the health status of patients and reduce viral load [17]. The mechanism of action has already been proven in other viral infections and involves: 1) induction of adaptation to oxidative stress, with restoration of the balance of the redox state of the cells; 2) induction of IFN-y and pro-inflammatory cytokines; 3) increased blood flow and oxygenation of vital organ tissues; 4) in addition to being able to act as an autovaccine when administered systemically in the form of autohemotherapy [17].

This is a time of vigilance, common sense and scientific investigation [2]. Some clinical studies using ozone therapy are being carried out in China and Italy to determine the effectiveness of this procedure as an adjuvant in the treatment of COVID-19 [18,19]. As there are no specific vaccines or pharmaceutical products for the treatment of this disease, the use of integrative and complementary practices, after a careful assessment of risks and benefits, can assist in the development of protocols to control the infection and disorders caused by SARS-CoV-2.

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