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Ozone therapy and SARS-CoV-2 infection

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Abstract

Ozone is an atmospheric gas occurring in very low quantities. It is formed in parallel with dissociation in the atmosphere. Artificial ozone sources produced in the laboratory are important for its therapeutic effect - virucidal effect, bactericidal effect, fungicidal effect and anti-parasitic effect, as well as for its biocide disinfectant effect.

Ozone therapy can be used in the treatment of the SARS-CoV-2 infection, as non-pharmacologic complementary therapy alongside the pharmacologic therapy in the treatment of COVID-19. The effect mechanism of ozone therapy comprises the rebalancing of the redox homeostasis, induction of formation of IFN-γ and pro-inflammatory cytokines, increase of pulmonary, renal and cardiac vascularization and oxygenation; it acts like an auto-vaccine when administered as minor auto-hemotherapy.

Keywords: ozone, virucidal effect, complementary therapy in COVID-19.

Introduction

Ozone (O_3) is an unstable gas, a triatomic derivative of oxygen (O_2), occurring in the atmosphere in very low quantities - 0.03% or 5.3 x 10^{11} molecules/cm^3. It is formed by O_2 in the upper atmosphere layers at 25-30 km, in the area called ozonosphere where it reaches concentrations of 10-11ppm.

The atmospheric formation takes place under the influence of low wavelength UVC radiation. At ground level, O_3 can also arise under the influence of natural thunderstorms. Artificial sources of O_3 originate from the activity of UV radiations emitted by laboratory devices and physiotherapy devices, by the voltaic arc, by electric welding, etc. The ozonosphere plays an important role in shielding the biosphere from UVA and UVB radiations, which it absorbs up to 97-99%.

In parallel to O_3 formation, a dissociation process under the influence of infrared solar radiations and organic substances in the troposphere takes place, which can be converted to O_2.

The formation and decomposition processes of O_3 ensure a constant concentration between 0.1-0.5ppm, depending on altitude, latitude, season, solar activity, air movement. In high concentrations, O_3 is a pro-oxidant air pollutant with negative effects on the body, causing respiratory discomfort and ocular irritation.

The increase of fluor, chlorofluorocarbons, nitrogen oxides, freons in the atmosphere and their reactions with O_3 lead to the formation of holes in the O_3 layer, followed by the penetration of UV radiations affecting the tegument and often causing skin cancer and sunburns (Bocci, 2014).

Ozone effects

O_3 has favorable therapeutic effects on the body: bactericidal, virucidal, fungicidal, antiparasitic (Fernández-Cuadros et al., 2016; Fernández-Cuadros et al., 2020a; Kekez & Sattar, 1997; Martínez-Sánchez et al., 2020), immunomodulatory (Fernández-Cuadros et al., 2020b), stimulating the peripheral circulation (Ranaldi et al., 2020).

O_3 is recommended in the treatment of: wounds,

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gangrenes, certain locomotor conditions (arthritis, rheumatoid arthritis, osteoarthritis); respiratory diseases (pneumonias, cancers and pulmonary fibrosis, bronchiectasis, asthma, chronic obstructive pulmonary disease); cardiovascular diseases (myocardial infarction, coronary heart diseases, arterial diseases of the lower limbs); neurological diseases (multiple sclerosis); type II diabetes (diabetic retinopathy, diabetic foot infections); hepatitis C (Fernández-Cuadros et al., 2020b; Cattel et al., 2021; Izadi et al., 2021).

O_3 also has a disinfectant role with biocide effect. The maximum antiviral disinfectant effect requires a short period of relative humidity above 90% and an O_3 concentration of 20-25 ppm, 39-49 mg/m^3 (***, 2020).

It is used for water disinfection, ground decontamination, disinfection of interiors, human (equipment) and animal decontamination, decontamination of hard surfaces (plastic, glass, stainless steel), fabrics, food processing (Fernández-Cuadros et al., 2016; Percivalle et al., 2021; ***, 2020). For this purpose, it is used as a gas, liquid spray and aerosols (Percivalle et al., 2021). A 30 second exposure to O_3 inactivates viruses up to 99% (Roy et al., 1981; Percivalle et al., 2021).

SARS-CoV-2 infection

During the history of mankind, many infectious diseases have led to pandemics, the last one being caused by the new coronavirus SARS-CoV-2, which is responsible for the disease called Coronavirus disease 19 (COVID-19).

Shi et al. (2020) described four stages of SARS-CoV-2 infection. In stage I, the asymptomatic or incubation period, the virus can or cannot be detected; 85% of patients can remain asymptomatic (Senniapan et al., 2020). In stage II or the non-severe symptomatic period, the virus can be detected, as it is present at the level of the upper respiratory tract; during this stage, flu-like symptoms, acute infection of the upper respiratory tract or digestive symptoms may appear. Stage III or the severe respiratory period comes with high viral load. Patients have pneumonia (frequently alongside cough and fever), with or without hypoxemia (SpO2 < 92%), and thoracic injuries visible by CT; 5% of the patients can present severe symptoms (Senniapan et al., 2020). Stage IV or the critical stage is the stage of complications, which can lead to death: acute respiratory distress syndrome (ARDS) characterized by the presence of shock, encephalopathy, myocardial injuries occur, also cardiac insufficiency, coagulation disorders and acute renal dysfunctions; the mortality rate can reach up to 2.8% (Senniapan et al., 2020).

Ozone therapy and SARS-CoV-2 infection

Ozone therapy is a non-pharmacologic therapeutic procedure, consisting of administering a mixture of O_2 and O_3 or Medical Ozone using the technique of auto-hemo-infusion (Ranaldi et al., 2020), with a content of 97% O_2 and 3% O_3 (Hernández et al., 2021). O_3 is considered an adjuvant treatment within the antiCOVID-19 therapy (Araimo et al., 2020) with cytoprotective role (Martínez-Sánchez et al., 2020).

O_3 can be administered as part of the treatment as saline ozone solution preventively or interventionally (***, 2020), as major auto-hemotherapy (***, 2020; Hernández et al., 2021), as extracorporeal blood oxygenation and ozonation (O_2 and O_3 mixture) (Ricevuti et al., 2020), as minor auto-hemotherapy (Hernández et al., 2021) and rectally (Fernández-Cuadros et al., 2020b).

It is recommended due to the anti-inflammatory, immunomodulatory, organ-protective validity (Ricevuti et al., 2020). Standard dosages and methods are established according to the *Madrid Declaration on Ozone Therapy* (Schwartz-Tapia et al., 2015 quoted by Martínez-Sánchez et al., 2020).

O_3 treatment recommended for COVID-19 patients

The severity of SARS-CoV-2 infection depending on the clinical symptomatology, para-clinical signals and treatment was described by Fernández-Cuadros et al. (2020a) in three stages. In stage 1 - early infection, with strong viral response, symptomatology is generally light and it is represented by fever, dry cough, diarrhea, headache, while para-clinical lymphopenia, increased prothrombin time, a slight LDH increase appear; during this stage, O_3 acts like a viral inhibitor (virucidal effect). In stage 2 - the pulmonary stage, without hypoxemia (2a) or with hypoxemia (2b), cytokine synthesis is initiated progressively. Dyspnea, abnormal radiological thoracic images appear, while the level of transaminases increases. During this stage, O_3 is administered as a cellular and humoral stimulant. Stage 3 – systemic hyper-inflammation, is characterized by the maximum level of cytokine storm. During this stage, severe acute respiratory syndrome (SARS), multiple organ failure syndrome (MOFS), shock, cardiac insufficiency occur. Para-clinically, this stage is characterized by an increase of inflammatory markers (LDH, CRP, IL-6); O_3 has an immunomodulatory action (decreasing IL-1, IL-6, IL-2, TNF-α and stimulating IL-10); O_3 blocks the pathway of the kβ (NF-kβ) nuclear factor and stimulates the pathway of the Nrf2 (nuclear factor erythroid 2-related factor 2) nuclear factor, while being beneficial within the cytokine storm and being able to favor O_2 distribution and hypoxemia, and showing benefits within MOFS.

The non-pharmacologic O_3 therapy in SARS-CoV-2 infection is paired with the pharmacologic therapy using remdesivir, chloroquine, hydroxychloriquine, combinations of lopinasivir and ritonavir, duranavir, danoprevir, cobicistat, Anti-CD147 Humanized Meplazumab, Recombinant Human Angiotensin-converting Enzyme 2, transfusions from recovering patients, NK cells, Umbilical Cord-Derived Mesenchymal Stem Cells, bevacizumab, eculizumab, immunoglobulin, vitamin C IV, vitamin D, INF-β, glucocorticoids (Martínez-Sánchez et al., 2020; ***, 2020). Besides the use as complementary therapy paired with the pharmacologic therapy, ozone therapy can also be used for disinfecting the environment, water and food (***, 2020).

Antiviral therapeutic effects of O_3 in COVID-19 therapy

O_3 can inactivate viruses present in biological fluids or intracellularly in pneumocytes, hepatocytes, alveolar

epithelial type II cells, CD4+ lymphocytes, monocytes, glial cells and neurons (Bocci, 2014).

Bocci & Paulesu (1990) consider that O_3 treatment can lead to the adaptation to oxidative stress (OS), by modulating the Nrf2 and NF-kβ factors and rebalancing the antioxidant environment; the antioxidant response of O_3 shows its paradoxical effect as a non-radical pro-oxidant, involved in the cellular redox state (Pecorelli et al., 2013; Izadi et al., 2021). O_3 can inactivate the virus directly by oxidizing its components or indirectly by generating O_2 species (ROS), generated because of its decomposition. The reactions between O_3 and ROS with the constituents of the virus structure (lipids, proteins and amino acids) determine the chain formation of other ROS, while the chain of oxidative processes contributes to the destruction of the viruses and the inhibition of the infectious mechanism, through the attack on the proteins and lipids of the SARS-CoV-2 spikes and envelope (Tizaui, 2020).

In the combination O_3 and O_2 (O_2O_3 therapy), by activating the Nrf2, the antioxidant response may increase the level of direct antioxidants (GSH, CO, bilirubin), the stimulation of GSH regeneration by GSH reductase and thioredoxin reductase, the increase of antioxidant and electrophilic enzyme levels (CAT, SOD, GPx, GSTr, NADPH-quinone oxidoreductase), the increase of enzyme level for stage II, inhibition of the inflammation mediated by cytokines though induction of leukotrien-B_4 12-hydroxydehydrogenase/15-oxo-prostaglandin 13-reductase. Also, the reduction of iron overload and of oxidative stress induced by ferritin occurs, as well as the repairing and restoration of proteins, protection against apoptosis and increase in DNA repairing activity (Sagai & Bocci, 2011).

The O_2O_3 mixture is highly soluble in plasma and induces the formation of secondary messengers, H_2O_2, ozonides and alkenes (Wan et al., 2020). The effect mechanism of O_2O_3 therapy on the proteasome, on the inflammatory cascade and the inflammatory process is by stimulating the Nrf2 nuclear factor and inhibition of the NF-kβ nuclear factor (Zhang et al., 2020). O_3 reacts with the double bond of the unsaturated fatty acids and generates aldehydes, which are lipid oxidation products (LOP) and reactive oxygen species (ROS), mechanisms that activate the biochemical means for increasing the vascular flow in ischemic areas (Bocci, 2005 quoted by Ranaldi et al., 2020). O_3 and other compounds resulting from ozonation can stimulate the production of certain growth factors in platelets and tissues (Vallacchi et al., 2011).

O_3 therapy can induce the synthetization of pro-inflammatory cytokines such as IL and IFN-gamma (IFN-γ) in the monocyte-macrophage system and the activation of antigen-presenting cells (Larini & Bocci, 2005). Tissue irrigation and oxygenation increase at cardiac level (Simonetti et al., 2019), hepatic level (Tezcan et al., 2018), pulmonary level (Kaldirim et al., 2014) and renal level (Wang et al., 2014). O_3 acts upon the microcirculation: arterioles, meta-arterioles, precapillary sphincters, true capillaries and/or thoroughfare channels and venules, vessels with a caliber under 100 μm (Liu et al., 2015). The effect takes place through direct or indirect generation of mediators, with effect on the endothelial, pericyte and erythrocyte cells.

O_3 can act like an auto-vaccine, which can induce the oxidation of the viral components (Bocci, 2014; Bocci et al., 2009).

Mediators involved in ozone therapy

Hydrogen peroxide, oxygenated water (H_2O_2) is a non-radical reactive O_2 species, which increases in plasma after ozone therapy. Oxygenated water stimulates neoangiogenesis through the formation of the vascular endothelial growth factor (VEGF), which activates mediators playing a role in coagulation, complement formation and generation of inflammatory cells. In addition, it increases the concentration of 2.3-diphosphoglycerate (2.3-DPG) and oxygenation in peripheral tissues, if transferred into the red blood cells and reduced to water through the antioxidant glutathione system (GSH) - catalase (CAT). Another effect is the reduction of thrombotic and fibrotic processes (Ranaldi et al., 2020).

4-hydroxynonenal or 4-hydroxy-2-nonenal (4-HNE) is the most active aldehyde occurring after ozone therapy. It acts as a major mediator in the transduction of cellular signals, activating the synthesis of certain protective enzymes (γ-glutamate, cysteine ligase, γ-glutamyl transferase, γ-glutamyl transpeptidase, heme oxygenase-1 – HO-1), as well as the synthesis of some antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), catalase (CAT) (Esterbauer et al., 1991; Bocci et al., 2011).

Nitric oxide (NO) is a radical species of nitrogen. O_3 induces the synthesis of nitric oxide synthase (NOS) and the formation of NO. It is produced by endothelial cells, neutrophils, macrophages, fibroblasts, platelets, neurons (Green, 2020).

NO has many effects on the cardiovascular system, as well as on the nervous system (Green, 2020). In the cardiovascular system, NO has a local endothelial effect on vasodilator tone, the modulation and proliferation of smooth muscle fibers, on endothelial permeability, and a local effect on platelets through prevention of platelet deposits, lubrication of the vascular wall and modulation of aggregation, an antithrombotic effect. NO modulates the control mechanisms of vascular tone through local release of endothelin I and serotonin, with vasoconstrictor effect. In addition, it has a general effect of maintaining normal blood pressure and induces the increase of HO-1 level by activating Nrf2.

In the nervous system, NO has local effects on the nervous tissue as a synaptic neuromediator.

Heme oxygenase-1 (HO-1) is an indirect NO product, an enzyme which converts heme to CO, which inhibits the NF-kβ pathway, reduces the expression of inflammatory cytokines, by inhibition of cytokines and chemokines (IL-1β, IL-8, IL-33, MCP-1 and MIP-1β) and activates anti-inflammatory cytokines (IL-10).

NADPH-quinone oxidoreductase (NQO-1) is a detox enzyme from stage II, efficient in the Nrf2 regulation of reduced nicotine-adenine-dinucleotide phosphate (NADPH) and reduced nicotine-adenine-dinucleotide (NADH). It contributes to the regulation of the redox balance, by modulating the ratio of reduced/oxidized

pyridine nucleotides (Ranaldi et al., 2020).

O_3 administration blocks the inflammatory processes by linking NF-kβ and Nrf2 (*nuclear factor erythroid 2–related factor 2)*. The two factors are part of a network of regulatory protein transcription factors, which modulates the expression of genes associated with inflammatory response.

NF-kβ initiates the transcription of genes linked to pro-inflammatory cytokines. Ozone therapy has anti-inflammatory and anti-apoptotic effects by blocking the activity of this factor (Cooke, 1997) and stimulates the activation of the Nrf2 pathway (Re et al., 2014).

Conclusions

1. Ozone therapy can be used in the treatment of SARS-CoV-2 infection.

2. The effect mechanism of ozone therapy comprises the rebalancing of the redox homeostasis, induction of the formation of IFN-γ and pro-inflammatory cytokines, increase of pulmonary, renal and cardiac vascularization and oxygenation; it acts like an auto-vaccine when administered as minor auto-hemotherapy.

3. Ozone therapy is a non-pharmacologic method, which can be used as complementary therapy paired with the pharmacologic therapy in COVID-19 treatment.

Conflict of interests

The authors declare no conflict of interest.

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