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REVIEW ARTICLE

Ozone therapy in COVID-19: an integrative review

Ozonoterapia en COVID-19: una revisión integradora

Ozonioterapia na COVID-19: uma revisão integrativa

Sonia Regina Jurado[1]
ORCID: 0000-0002-7220-4083
Camila dos Santos Paiz[1]
ORCID: 0000-0001-6415-7478
Ieda Maria Gonçalves Pacce Bispo[1]
ORCID: 0000-0001-7490-6903
Mara Cristina Ribeiro Furlan[1]
ORCID: 0000-0003-3227-7074
Thais Carolina Bassler[1]
ORCID: 0000-0001-6964-4494
Andrea Sanchez[1]
ORCID: 0000-0002-60265508

[1]Universidade Federal do Mato Grosso do Sul. Mato Grosso do Sul, Brazil.

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Corresponding author:
Sonia Regina Jurado
E-mail: srjurado@bol.com.br

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Abstract

The aim was to demonstrate the available evidence on ozone therapy in patients with COVID-19 and its therapeutic applicability through hospital protocols. This is an integrative review, carried out in PubMed and LILACS search sources, from 2011 to 2021. 87 articles were identified, but 11 articles were selected that suited the studied theme. The literature studied indicated that ozone exerts antiviral activity by inhibiting viral replication and direct inactivation of viruses. It is also an adjuvant to antiviral drugs. Combined treatment with ozone and antivirals has been shown to reduce inflammation and lung damage. The routes of ozone administration were systemic (rectal) and autohemotherapy. Conclusions: Ozone therapy is an adjuvant therapy to antiviral treatment in COVID-19-positive patients, in addition to being economically viable and easy to administer.

Descriptors: Coronavirus Infections; Ozone; Infection SARS-CoV-2; COVID-19 Virus Infection; Immune System.

Resumén

El objetivo fue demostrar la evidencia disponible sobre la ozonoterapia en pacientes con COVID-19 y su aplicabilidad terapéutica a través de protocolos hospitalarios. Esta es una revisión integradora, realizada en PubMed y fuentes de búsqueda LILACS, de 2011 a 2021. Se identificaron 87 artículos, pero se seleccionaron 11 artículos que se adecuaban al tema estudiado. La literatura estudiada indicó que el ozono ejerce actividad antiviral al inhibir la replicación viral y la inactivación directa de los virus. También es un adyuvante de los medicamentos antivirales. Se ha demostrado que el tratamiento combinado con ozono y antivirales reduce la inflamación y el daño pulmonar. Las vías de administración del ozono fueron sistémica (rectal) y autohemoterapia. Conclusiones: La ozonoterapia es una terapia adyuvante al tratamiento antiviral en pacientes positivos para COVID-19, además de ser económicamente viable y fácil de administrar.

Descriptores: Infecciones por Coronavirus; Ozono; Infección por Coronavirus 2 del SARS; Infección por el Virus COVID-19; Sistema Inmunológico.

Resumo

Objetivou-se demonstrar as evidências disponíveis sobre ozonioterapia em pacientes com COVID-19 e sua aplicabilidade terapêutica por meio de protocolos hospitalares. Trata-se de uma revisão integrativa, realizada nas fontes de busca PubMed e LILACS, no período de 2011 a 2021. Foram identificados 87 artigos, mas, selecionados 11 artigos que se adequaram à temática estudada. A literatura estudada apontou que o ozônio exerce atividade antiviral por meio da inibição da replicação viral e da inativação direta dos vírus. Também é um adjuvante às drogas antivirais. O tratamento combinado com ozônio e os antivirais demonstrou redução da inflamação e dos danos pulmonares. As vias de administração do ozônio foram sistêmica (retal) e auto-hemoterapia. Conclusões: A ozonioterapia é uma terapia adjuvante ao tratamento com antivirais em pacientes COVID-19-positivos, além de ser viável economicamente e de fácil administração.

Descritores: Doença pelo Novo Coronavírus; Ozônio; Infecção pelo SARS-CoV-2; Infecção Viral COVID-19; Sistema Imunológico.

Introduction

In early December 2019, a cluster of pneumonia cases of unknown cause was identified in Wuhan, China. Research revealed that these cases resulted from infection with a new coronavirus, initially named COVID-19 and subsequently Coronavirus Severe Acute Respiratory Syndrome 2 (SARS-CoV-2). The infection quickly spread through China and spread to Thailand and Japan, and within a short period infected thousands of people worldwide[1].

In symptomatic adult patients, the clinical manifestations of the disease consist of fever, cough, nasal congestion, fatigue, and other signs of upper respiratory tract infections, and may progress to severe illness with dyspnea and severe chest symptoms corresponding to pneumonia in approximately 75% of patients[2].

COVID-19 predominantly involves the lungs, where diffuse alveolar damage occurs with microcirculation involvement and, consequently, marked hypoxia. The dysregulation of the immune response is associated with the lymphocytopenia present in the vast majority of these patients. There is also a cytokine storm characterized by increased plasma concentrations of ferritin, C-reactive protein, interleukins (IL) − 1β, IL-6, IL-12, tumor necrosis factor and interferon-γ[3].

Among the different therapies for COVID-19, the use of steroids and antiviral or immunomodulatory treatment (remdesivir, hydroxychloroquine and tocilizumab) stand out)[4].

More recently, there has been increasing interest in ozone therapy due to modulation of cytokines and interferons. Ozone therapy in patients with COVID-19 can be used as monotherapy or as an adjunct to standard treatment regimens. Therefore, there is growing interest in the role of ozone therapy in the treatment of patients with COVID-19[5].

Ozone (O3) is a gas composed of 3 oxygen atoms, including a stable pair (O2) and a third, unstable atom, which gives ozone its beneficial effects. Medical ozone generators produce 1-5% ozone gas in 95-99% pure oxygen. For therapeutic purposes, concentrations of 10-70 µg/mL are commonly used[5, 6].

Ozone therapy has been known for over 150 years and is particularly used in the treatment of infectious diseases in countries such as Cuba, Italy, Germany, Russia and Spain[7]. In Brazil, ozone therapy is considered an integrative complementary treatment by Ordinance No. 702, of March 21, 2018 and is offered by the Unified Health System (SUS)[8]. The Federal Nursing Council (COFEN) regulated ozone therapy as a nursing practice in Brazil through Normative Opinion No. 01, of February 20, 2020[9]. However, this integrative practice has not yet received approval from the Federal Council of Medicine (CFM).

Among the therapeutic effects of ozone, it includes greater supply of tissue oxygen due to the increase of 2,3-diphosphoglycerate (responsible for transferring O2 from hemoglobin to tissues), reduction of platelet aggregation and analgesic effect[6, 10,11,12].

Ozone also has other proven biological properties: (a) antiviral, (b) modulation of inflammatory interleukins (IL-1, IL-6, TNF-α), (c) antioxidant (via Nrf2), (d) anti-inflammatory (blocking NRLP3 inflammasome), (e) anticoagulant (antithrombin III effect), and (f) vasodilator effect (NO release)[6,13,14].

Regarding COVID-19, medicinal ozone decreases lung inflammation, prevents viral growth, regulates pulmonary circulation, prevents microvascular thrombosis, improves tissue hypoxia, improves phagocytic function, and modulates immune function with the inhibition of inflammatory mediators[5].

Thus, the present study aimed to describe the effects of ozone therapy in the treatment of patients with COVID-19.

Methodology

The integrative bibliographic review was carried out in October and November 2021 and included international publications from January 1, 2010 to October 30, 2021.

The bibliographic review was carried out in the LILACS and Pubmed databases, using the following descriptors in English: “ozone”, “COVID-19” and “Severe Acute Respiratory Syndrome”, joining them with Boolean operators “AND” and “OR” .

The guiding question was: What are the effects of ozone therapy in the treatment of patients with COVID-19?

Inclusion criteria were: articles published in journals indexed in the aforementioned databases, works available in full, published in English or Spanish, descriptive, experimental, observational, retrospective, case-control and case studies that answered the guiding question.

Works in duplicates were excluded; texts not available in full; letter to the editor; bibliographic review works; dissertations; theses and scientific articles in a language other than English and Spanish and those that did not fit the theme.

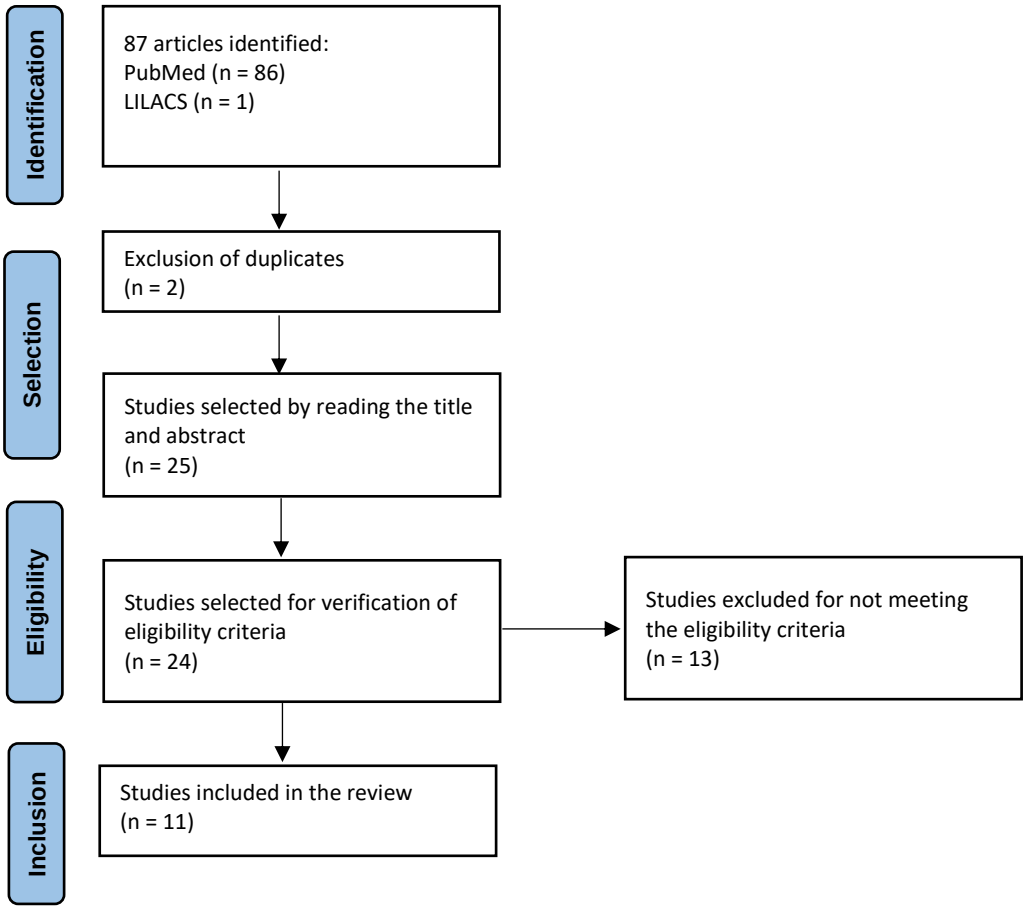
In order to organize the data collected through the bibliographic review, a form was prepared, containing the following information: year, author, type of study, sample and main clinical findings.

Results

A total of 87 articles were selected, coming from PubMed (n= 86) and LILACS (n= 1) search sources. However, the final sample consisted of 11 articles (Figure 1).

Selected articles, description of ozone therapy treatments and clinical outcomes of patients with COVID-19 are listed in Chart 1.

Figure 1. Study search and selection flowchart. Três Lagoas, MS, Brazil, 2011-2021



Source: Adapted from Moher and collaborators[15].

Chart 1. Selected articles. Três Lagoas, MS, Brazil, 2011-2021

Year	Authors	Study	Sample	Ozone therapy	Standard treatment	Clinical outcomes
2020	Tascini *et al.*[17]	Case Control	Ozone group (n= 30) and control group (n= 30)	Autohemotherapy 200 ml of O2-O3 (40 µg/mL) + 200 ml of autologous blood, performed daily for 3 days in a row.	Antiretroviral therapy (lopinavir/ritonavir: 2 tablets every 12 hours, darunavir/cobicistat: 1 tablet daily), hydroxychloroquine 400 mg every 12 hours on the first day, followed by 200 mg every 12 hours for another 4 days, tocilizumab 10 mg/kg single dose, amiodarone, azithromycin, other antibiotics and steroids.	In the ozone group, 7% of patients experienced worsening compared to 17% in the control group. In the ozone group, there were no deaths while in the control group there were 2 deaths..
2020	Wu *et al.*[21]	Case study	4 patients (age range 56-77 years)	Autohemotherapy with O3 concentration of 40 µg/mL per 100 mL of blood. From 1 to 9 sessions were administered in the 4 patients, according to the severity of the case.	All 4 patients received antiviral agents, comprising lopinavir/ ritonavir and interferon-alpha, and 3 patients were treated with steroids.	All showed a decrease in inflammatory biomarkers and an improvement in the ground-glass aspect of the CT findings of the lungs.
2020	Colak *et al.*[7]	Case Control	Ozone group (n= 37) and control group (n= 38)	Autohemotherapy 100 ml of O2-O3 (30 µg/mL) + 100 ml of autologous blood, performed daily for 7 days.	Hydroxychloroquine (400 mg every 12 hours for the first day and 200 mg every 12 hours for the next 4 days), enoxaparin, favipiravir, and antibiotics for secondary bacterial infection, and antipyretics if needed.	The mortality rate was 5.4% for the ozone group and 27.8% for the control. The ICU admission rate was also lower in the ozone group (16.2%) when compared to the control group (22.2%).
2020	Araimo *et al.*[22]	Case Control	Ozone group (n= 14) and control group (n= 14)	Autohemotherapy 250 ml of O2-O3 (30µg/ml) + 250 ml of autologous blood, 2 times a day.	Antivirals (lopinavir/ritonavir) azithromycin, hydroxychloroquine, tocilizumab in case of increased IL-6 or worsening respiratory function.	The 30-day mortality was 8.3% for the ozone group and 10% for the control. Ozone therapy did not significantly influence inflammation markers, hematological profile and

					Prebiotic supplementation (Thermophilus, Bifidobacterium lactis, Lactobacillus, acidophilus, Lactobacillus helveticus, Lactobacillus paracasei, Lactobacillus plantarum, Lactobacillus brevis), 2 times a day, for 7 days.	subpopulations of lymphocytes from treated patients.
2020	Franzini *et al.*[12]	Clinical	50 patients	Ozonized autohemotherapy 200 mL of autologous blood (O3 45 µg/mL) from 3 to 5 days.	Azithromycin/azobactam (500 mg/day for 6 days) Hydroxychloroquine (200 mg/day for 7 days); Methylprednisolone (50-100 mg/day for 7 days); Enoxheparin (Clexane®) (40-60 mg/day, customized to the patient's clinical status); Ascorbate (1000 mg/day).	Reduction of inflammatory and thromboembolic markers (C-reactive protein, IL-6, D-dimer). Improvement in major respiratory indices.
2020	Hernández *et al.*[6]	Case study	3 patients, 2 men aged 49 and 69 years and 1 woman aged 64 years	Ozonized autohemotherapy 200 ml of autologous blood + 200 ml of O3 at a concentration of 45µg/mL. Two sessions of autohemotherapy were carried out twice a day, in three days.	Authors did not mention the drugs used in the standard treatment.	Decrease in inflammatory and thromboembolic markers (D-dimer, lactate dehydrogenase and C-reactive protein).
2020	Pena-Lora; Albaladejo-Florín; Fernández-Cuadros[20]	Case study	Female patient, 84 years old, with comorbidities (hypertension, Type 2 diabetes mellitus, heart failure, hypertensive cardiomyopathy, chronic obstructive pulmonary disease, pulmonary nodule with metabolic criteria for malignancy)	Rectal ozone 100 mL with O3 at a concentration of 35 µg/mL (5 sessions, 1 session every 24 hours).	Corticosteroid therapy.	Parameters before and after ozone therapy: D-dimer = 2303 vs 398 ng/ml; ferritin = 302 vs 152 ng/ml; lactate dehydrogenase = 327 vs 195 U/L; IL-6 = 136.1 vs 9.28 pg/ml; RT-PCR SARS-COV-2 positive vs. negative. Improved lung x-ray (decreased ground-glass appearance).
2021	Hernández *et al.*[5]	Case Control	Ozone group (n= 9) and control group (n= 9)	Ozonated autohemotherapy 200 ml of autologous blood + 200 ml of O3 at a concentration of 40µg/ml. 2 sessions were performed per day, for 5 days.	Ceftriaxone 2 g/day for 5 days, levofloxacin 500 mg/12h, hydroxychloroquine 400 mg/day for 4 days, dexamethasone 6 mg/day for 10 days or methylprednisolone 40 mg/12h and azithromycin 500 mg/day for 3 days. Enoxaparin 1 mg/kg every 12 hours as therapy of anticoagulation.	Comparing the control and ozone groups, there was a decrease in the values of biological markers: lactate dehydrogenase (506 vs. 487 U/L); ferritin (556 vs 290 µg/L) and D-dimer (943 vs 389 ng/mL
2021	Shah *et al.*[25]	Case Control	Ozone group (n= 30) and control group (n= 30)	Rectal insufflation with 150 mL of O3 (40 µg /mL) 2 times a day and minor autohemotherapy, with 2-3 mL of venous blood with 5 mL of ozone at 25µg/ mL, for 10 days.	Hydroxychloroquine 400 mg/day on the 1st day and 200 mg/day for the following 4 days: Methylprednisolone 0.5 to 1 mg/kg for 3 days and Enoxaparin 40 mg/day.	In the ozone-treated group there was a reduction in all three inflammatory biomarkers. The ozone group had no need for supplemental oxygen, ICU admission and mechanical ventilation, while in the control group 10% of patients required mechanical ventilation, ICU admission and 2 died.
2021	Fernández-Cuadros *et al.*[27]	Case Control	Ozone group (n = 14) and control group (n = 14)	The ozone protocol consisted of 8 sessions (1 session/day) of intrarectal ozone (150 mL volume, at a concentration of 35 µg/mL.	Antivirals (remdesivir), corticosteroids (dexamethasone / methylprednisolone), monoclonal antibodies (Anakinra / Tocilizumab), antibiotics	Ozone treatment improved O2 saturation and decreased O2 supply. Inflammation biomarkers (D-dimer, lactate dehydrogenase, C-reactive protein, IL-6 and ferritin)

					(Azithromycin) and anticoagulants (Enoxaparin).	decreased in both groups, but only significantly in favor of the ozone group (p<0.05). Mortality and length of stay, although not significant, they were lower in the ozone group.
2021	Sozio *et al.*[24]	Case Control	Ozone group (n= 48) and control group (n= 44)	Ozonized autohemotherapy 200 ml of autologous blood + 200 ml of O3 at a concentration of 35μg/mL, for 3 consecutive days.	Antiretroviral therapy (lopinavir/ritonavir 200/50 mg 2 tablets every 12 hours or darunavir/cobicistat 800/ 150 mg 1 tablet per day) and hydroxychloroquine 400 mg every 12 hours on the first day, followed by 200 mg every 12 hours for 4 consecutive days.	Adjunctive O2-O3 therapy did not show any effects on mortality or mechanical intubation, but showed clinical improvement at day 7.

Note: RT-PCR: Reverse Transcriptase Reaction followed by Polymerase Chain Reaction (RT-PCR); ICU: Intensive Care Unit.

Discussion

Ozone can be applied by different routes according to the desired treatment. The methods of clinical administration of ozone can be subcutaneous, intramuscular, intradiscal, intracavitary (peritoneal and pleural spaces), intravaginal, intraurethral and vesical and ozonized autohemotherapy, however direct inhalation of ozone gas (0.1 to 1 ppm) can be toxic to the upper respiratory tract. Autohemotherapy (AHT-O3) requires taking a predetermined blood sample (100-200 mL) which is added at a 1:1 ratio of O2-O3, at a concentration of 30-40μg/mL of ozone and, infused in the patient[16,17].

The mechanisms of action of ozone involve two fundamental biochemical processes that occur in blood plasma: an immediate reaction where there is the production of reactive oxygen species (ROS) which is largely inactivated by the antioxidant system and a delayed reaction, which lasts few seconds and consumes the remaining, tiny amount of the total dose of ozone applied, where there is the formation of hydrogen peroxide (H2O2), various aldehydes, ozonides (various molecules resulting from reactions with fat, carbohydrates, fatty acids, among others) and lipoperoxides which are products of lipid oxidation (LOPs)[18].

These products, with free radical activities, at submicromolar concentrations, are capable of inducing an antioxidant response in the body itself, based on endogenous-enzymatic mechanisms. From these mechanisms, the therapeutic effects result from the action of ROS and LOPs on the most varied cells and organs of the organism and not from a direct action of ozone. ROS act on red blood cells, restoring the rheological properties of blood and aerobic glycolysis, increasing oxygen transport and ATP production. LOPs, in turn, stimulate endothelial cells to produce nitric oxide (NO) in therapeutic concentrations that benefit the correction of disorders in blood vessels. In the bone marrow, they promote the release of stem cells and, in several other organs, the regulation of antioxidant enzymes and cytokines[5,19].

Studies support the use of ozone as an antiviral, stimulator of cellular immunity, anti-inflammatory, antioxidant and stimulator of oxygenation in hypoxic tissues. These properties allow its use as an adjunct to standard COVID-19 treatment (oxygen therapy, hydroxychloroquine, lopinavir/ritonavir, methylprednisolone, and broad-spectrum antibiotics)[5,7,12,17,20-25].

Three evolutionary stages are recognized in SARSCoV-2 infection: (a) stage 1 (initial infection); (b) stages 2a and b (normoxic and hypoxic pulmonary phase); and (c) stage 3 (systemic hyperinflammation or “cytokine storm”)[26]. In this scenario, Fernández-Cuadros et al.[27] considered four biological properties of ozone (O3) that could act in the different stages of SARS-CoV-2 infection. (A) Ozone can inactivate the virus by direct (O3) or indirect oxidation - ROS and LOPs. (B) Ozone can stimulate the humoral and cellular immune system. Properties A and B may be useful in the early phase of COVID-19 infection (stages 1 and 2a). (C) Ozone reduces inflammation and modulates the antioxidant system, making it useful in the hyperinflammation or "cytokine storm" phase. (D) Ozone improves gas exchange. Properties C and D make ozone useful in the phase of hypoxemia and/or multi-organ failure (stage 2b and stage 3).

According to Sozio et al.[24], ozone therapy is very useful in the initial phase of the development of SARS-CoV-2 when blood oxygenation is hampered by interstitial edema and fluid exudation into the alveoli, leading to ventilation/perfusion mismatch. These authors did not demonstrate any effects of ozone on mortality or mechanical intubation in patients with COVID-19, but they did reveal clinical improvement in these patients on day 7 of treatment.

A total of 11 articles including patients affected by COVID-19 and treated with ozone therapy were found in the peer-reviewed and indexed scientific literature. Three studies addressed rectal ozone therapy in the treatment of patients with SARS-CoV-2[20,25,27]. Pena-Lora et al.[20] treated an elderly patient with COVID-19 with daily rectal ozone therapy (100 mL volume and concentration 35 μg/mL). Fernández-Cuadros et al.[27] administered rectal ozone therapy to 14 patients with COVID-19 daily, for 8 days, with a volume of 150 ml and concentration 35 μg/mL. Shah et al.[25] associated minor autohemotherapy with rectal ozone insufflation in 30 patients, 150 mL, at a concentration of 40μg/mL.

However, most studies (n=8) addressed ozonized autohemotherapy in the treatment of SARS-CoV positive individuals [5,6,7,12,17,21,22,24]. The findings of rectal insufflation with ozone for the treatment of patients with COVID-19 are similar to those of ozonized autohemotherapy[20,25,27].

Ozone in COVID-19 patients prevents viral replication because it activates Nrf2 which blocks SARS-CoV-2 S protein fusion with the ACE2 receptor[6]. Regarding viricidal activity, ozone is capable of easily oxidizing cysteines and tryptophans present in the spike proteins of the Coronavirus. Cysteine residues, abundant in viral envelope proteins and essential for host cell entry, are also targets for palmitoylation. These mechanisms are able to directly attenuate SARS-CoV-2 infection and result in faster recovery from pneumonia in infected individuals[25].

One of the best ways to avoid a poor prognosis in patients with COVID-19 is to promote a rapid reduction in the viral load[28]. Antiviral treatment decreases pulmonary infiltrates and damage to lung tissue. Shah et al.[25], studying 60 SARS-CoV-2 patients and allocated into two groups: control (n= 30) and ozone (n= 30), detected that 77% of individuals in the ozone group had the reverse transcriptase reaction followed by the chain reaction RT-PCR negative on day 5 and 100% were RT-PCR negative on day 10. This clearly points to the advantage of faster virus eradication that can be attributed to the antiviral potential of ozone therapy.

In the vast majority of studies, there was a decrease in inflammatory molecular biomarkers, such as IL-6, C-reactive protein, lactate dehydrogenase and ferritin in the groups of patients treated with ozone compared to those treated with standard medication. However, the study of Tascini et al.[17] did not reveal IL-6 decrease in the ozone group, as this group had more severe COVID-19 conditions compared to the control group. However, it showed clinical improvement of 53% and no deaths in the ozone group, while it showed 33% improvement in clinical conditions and 2 deaths (7%) in the control group.

In addition, the O2-O3 mixture has an antithrombotic effect because it modulates the D-dimer. D-dimer, also known as D-dimer, is one of the breakdown products of fibrin, which is a protein involved in clot formation[6]. Thus, when there are changes in the coagulation process, it is possible that there is a greater amount of circulating D-dimer. This is usually increased during COVID-19 and has been shown to decrease in patients treated with ozone therapy[5,6,12,20,27].

Increased values of the hepatic enzyme lactate dehydrogenase (LDH), C-reactive protein and serum ferritin have often been associated with a worse prognosis for patients with COVID-19[29,30]. Intensive monitoring of liver tests can help predict the prognosis of the patient with COVID-19. When talking about the increase in LDH, this may be related to damage to organs such as the liver[31]. Ozone therapy used as an adjunct to standard COVID-19 treatment has been shown to reduce LDH levels[5,6,20].

The study of Shah et al.[25] revealed a greater reduction of biological markers in the ozone group, being 21.29%, 30% and 25% in the levels of C-reactive protein, LDH and ferritin. Despite the reduction of these parameters in the ozone group, there was no statistical difference between the ozone and control groups. Another study showed a reduction of around 50% in ferritin, C-reactive protein and D-dimer in the group treated with ozone when compared to the control[5].

Ozone has potent anti-inflammatory properties through modulation of the NLRP3 inflammasome, which plays a crucial role in the initiation and persistence of inflammation in various diseases[32]. Ozone can also confer renal protection as it modulates the accumulation of neutrophils locally, the expression of IL-6, tumor necrosis factor (TNF)-α and albumin modified by ischemia in the kidneys, and increases the local antioxidant capacity[33].

Ozone is capable of inducing the release and modulation of IFN-γ, TNF-α and colony-stimulating factors, and modulates and stimulates phagocytic function which can have a very positive effect on COVID-19 infection[34-36].

On the study of Shah et al.[25] which compared the control group treated with standard medication for COVID-19 and the ozone group, it was observed that ozone reduced shortness of breath in 90% of cases on day 5. On day 10, the ozone group had 100% of individuals with improvement of shortness of breath and 91% in the control group ($p < 0.05$). Participants in the ozone group also did not require supplemental oxygen, ICU admission and mechanical ventilation, while the control group demonstrated that 10% of patients received mechanical ventilation and were admitted to the ICU, in addition to 2 deaths.

The study of Hernández et al.[5] detected clinical improvement in the first 7 days of treatment in 44% of patients who received ozonized autohemotherapy and 22% in the group treated with standard medication. After 14 days of treatment, there was a clinical improvement of 89% in the ozonated group and 33% in the control group. This indicates the need to integrate ozone therapy into existing care of patients with COVID-19, as ozone therapy not only reduces mortality, but also accelerates patient recovery, improves tissue oxygenation, and decreases lung damage[25].

Ozone therapy proved to be an excellent adjunctive therapy to the use of antivirals, reducing hospitalization time and treatment costs in patients with COVID-19. Wu et al.[21] compared the evolution of two severe cases of COVID-19. These sibling patients (patients 1 and 5) were admitted together on the same day. Both received antiviral treatments. Patient 1 was also treated with ozonized autohemotherapy and the length of stay in the ICU (10 days) and in the hospital (30 days) was shorter compared to patient 5. In addition, the cost of clinical treatment for patient 1 was $15,467 USD, but for his younger brother, Patient 5, the overall hospitalization cost was $139,935 USD.

ICU admission was required in 6 of 37 patients who were treated with ozone (16.2%), while 4 of 18 patients in the control group required ICU treatment (22.2%) ($p = 0.713$)[7].

The study of Araimo et al.[22] pointed out the need for cardiopulmonary resuscitation and admission to the ICU in two patients with COVID-19, one in the ozone group and the other in the control group. No deaths were observed among patients at 7 and 14 days of follow-up. However, the 30-day mortality was 7.1% (n=1) in both the ozone and control groups.

Pena-Lora, Albaladejo-Florín and Fernández-Cuadros[20] described the first case of rectal ozone use in an elderly patient with COVID-19 who had comorbidities such

as arterial hypertension, type 2 diabetes mellitus, heart failure, hypertensive cardiomyopathy, chronic obstructive pulmonary disease and pulmonary nodule with metabolic criteria of malignancy. Despite the associated diseases, the patient achieved improvements in the inflammatory markers of COVID-19 and in the radiographic appearance of the lungs after rectal ozone therapy was applied for 5 days. Even the RT-PCR SARS-COV-2 test was negative after ozone treatment.

The use of rectal ozone in patients with COVID-19 improved O2 saturation (94.30% vs 92.96%), reduced O2 supply, decreased inflammation biomarkers, and improved the Taylor radiological scale significantly when compared to standard treatment. In addition, ozone therapy decreased the length of stay (28.58 days ozone group vs 35.67 days control group)[27].

The mortality rate was also lower in the ozone group (8.3%) compared to the control group. (16,6%)[5,27]. Hernández et al.[5] reported a mortality rate of 11% for the ozone group and 22% for the standard care group. Tascini et al.[17] studied 60 patients with positive SARS-CoV-2, being a control group (n= 30) and ozone (n= 30), and did not detect any deaths in the ozone group, however, the mortality rate was 7% in the treatment group pattern. Colak et al.[7], comparing the mortality rates between the control and ozone groups, they identified a lower mortality rate in the ozone group (p = 0,032).

It is believed that rectal insufflation of ozone can lead to a modification of the intestinal microbial flora[37] and probiotic supplementation can help to correct this problem. Nonetheless, Araimo et al.[22] revealed no changes in gut flora using rectal ozone insufflation and lactobacillus supplementation in patients with COVID-19.

A high level of safety was found for ozonized autohemotherapy as well as rectal ozone insufflation in patients with COVID-19, since no adverse effects were reported in the studied literature.

More studies need to be carried out in order to corroborate the findings of this bibliographic review. Ozone concentration, route of administration (autohemotherapy or rectal insufflation), stage of the disease in which to administer it and patient selection are some of the aspects that need to be further discussed regarding the adjuvant use of ozone therapy in patients with COVID-19.

Conclusion

It has been noted that ozone therapy, both in the form of autohemotherapy and rectal insufflation, is very useful as an adjunctive treatment in COVID-19, as it improves immunity; reduce length of stay and mortality rate; reduce inflammatory biological markers, reduce viral load, have a virucidal effect, decrease tissue hypoxemia, improve oxygen saturation, reduce oxygen supplementation, and improve ground-glass aspects of pulmonary findings.

Few scientific papers were found in the literature on ozone therapy in the treatment of SARS-CoV-2. Therefore, further studies are needed to better understand the clinical effects of ozone therapy in patients with SARS-CoV-2, in order to contribute to therapeutic decision making.

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