CASE REPORT

Effectiveness of Ozone Therapy on rapid radiologic and clinical recovery of a patient diagnosed with COVID-19

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ABSTRACT

SARS-CoV-2 is an RNA virus that can cause pneumonia leading to acute respiratory distress syndrome and pulmonary fibrosis (PF). Lung damage caused by COVID-19 can cause severe permanent respiratory failure. Ozone therapy (OT) is used as a complementary treatment during the COVID-19 pandemic. PF is one of the interstitial lung diseases, It is also radiologically identified in COVID-19 patients. In this case report, regression and healing on thorax CT findings are presented for a severe COVID-19 pneumonia-related intensive care unit patient who was diagnosed with PF on the post-COVID ward and treated with OT on the ward and even after discharge from hospital.

Key Words
COVID-19, Pulmonary fibrosis (PF), Ozone therapy, Antiviral

INTRODUCTION AND AIM

SARS-CoV-2, causing COVID-19, may cause severe acute respiratory tract diseases, progressing rapidly and severely in many patients it leads to mortality. Symptoms begin with high fever, headache, myalgia, and dry cough, continue with dyspnea and may lead to mechanical ventilation support requirements. SARS-CoV-2 is an RNA virus that may cause severe infection, pneumonia and fibrosis in the lower respiratory tract. The severity of the disease is linked to the efficacy of the immune system and infection and symptoms may progress rapidly if the immune system is weak (1).

At present, there is no medication that can treat COVID-19 infection. Therapeutic approaches aim to prevent side effects of the virus like inflammation and pulmonary fibrosis (PF), accepted to be among causes of death (1,2).

One of the treatments that may be beneficial is ozone therapy (OT), an effective treatment used for viral infections for many years without side effects It is cost effective and recommended as a complementary treatment for COVID-19 infection (3,4).

Ozone, a molecule containing three oxygen atoms, has bactericidal, virucidal and fungicidal activity. Ozone causes denaturation of virions with direct contact, disrupting the membrane lipids and lipoproteins of the virus. Changes to the

peplomer integrity in the membrane structure of the virus prevent viral binding and penetration, and disrupt binding to the host cell membranes. Ozone causes formation of lipid and protein peroxides in blood. These peroxides further reduce the viral load. Low doses of ozone display immune-stimulating effect, while higher doses display immune-inhibiting effect. The antiviral effect emerges with release of singlet oxygen from endogenously activated neutrophils in the antigen-antibody dynamic. This singlet oxygen and its products are strong oxidants and become the basic immunological agent in viral inactivation (5).

When the strong oxidant of ozone comes in contact with blood and other body fluids, it converts to reactive oxygen species (ROS) and lipid peroxidation products (LOP) responsible for biological outcomes. The main form of ROS is hydrogen peroxide (H2O2) which is easily transferred from plasma to cells. When H2O2 rises acutely above threshold concentrations in the cytoplasm of cells, in addition to many biological effects like antimicrobial, immune-stimulating and antioxidant effects, it becomes a triggering stimulant for simultaneous activations of erythrocytes, leukocytes and platelets through different biochemical pathways. H2O2 at higher concentrations is reduced to water by glutathione (GSH), catalase (CAT) and glutathione peroxidase (GSH-Px) enzymatic systems and the potential for harm reduces. Additionally, ozone has different biological effects. It increases tissue oxygenation by increasing oxygen release, and was shown to ease wound healing by increasing platelet-derived growth factor (PDGF) and transforming growth factor β (TGF- β). Ozone also may activate the immune system, and is accepted to increase interferon and interleukin-2 production and reduce tumor necrosis factor (TNF). Additionally, ozone both stimulates glycolysis in erythrocytes causing an increase in the amount of oxygen released to tissues and also increases the Krebs cycle increasing ATP production (6).

Ozone is effective on oxidation and inactivation of specific viral receptors used to create the binding structures in the cell membrane and as a result contributes to preventing ACE2 receptor-mediated cellular penetration in the first stage of viral infection. ACE2 receptor activity may be regulated and prevented by controlling the important nuclear message converter of nuclear factor erythroid 2-releated factor 2 (Nrf2). Ozone directly affects Nrf2 and prevents endogenous contact between the ACE2 receptors of SARS-CoV-2 blocking replication of COVID-19 (7). Ozone is a molecule with antiviral performance which interferes with the virus replication phase. This feature is connected to ozone's capability to oxidize cysteine residues (8).

Ozone stimulates both the humoral and cellular immune system, activates pathways linked to activated T cells and activated protein 1 transcriptional factors and induces transcription of genes linked to cytokines. For this reason, there is an increase in interferon-gamma and interleukin-2 production (9).

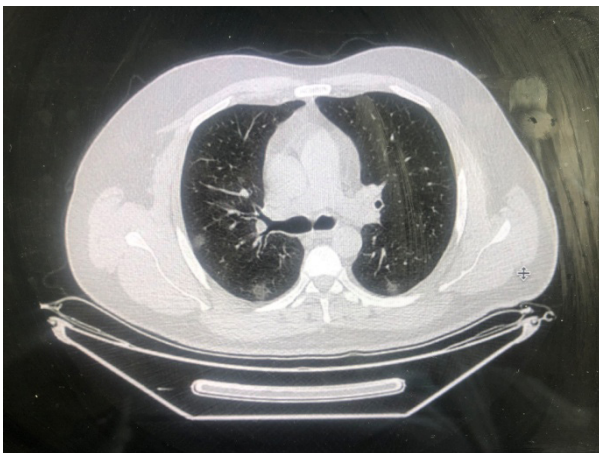
It is unknown whether the cause of fibrotic findings in the lungs is viral infection or treatment or ventilation or secondary to cytokine storm or a mixture of all of these (10). It is indicated that regression of fibrotic pathological findings in surviving severe COVID-19 patients may not be possible; however, prospective studies are required to identify long-term functional disorder (11). Fibrotic changes observed in mortal patients with long-term severe COVID-19 have only been

mentioned in brief in published studies and there is no full pathologic diagnosis for these cases (12). Typical radiologic findings of COVID-19 pneumonia are reported as interstitial inflammation and widespread consolidation (13).

In this case report we aim to present rapid improvement on radiological imaging of pulmonary involvement in our patient with severe COVID-19 pneumonia who received OT in addition to standard treatment in intensive care (IC) and only OT during ward follow-up after leaving the IC and after discharge at home.

CASE REPORT

A 46-year-old male patient with complaints of cough and fatigue attended the emergency service with accompanying respiratory distress. Physical examination found the patient had open consciousness, was oriented, Glasgow Coma Scale (GCS): 15, oropharynx mildly hyperemic and postnasal drip. Blood pressure (BP): 135/75 mmHg, peak heart rate (PHR): 86/min, FiO2: 0.12, SpO2: 99%, fever: 37 °C. Auscultation of the lungs found crepitant rales in bilateral lower zones and thoracic CT identified widespread ground glass appearance with patchy nodular character in lower lobes of both lungs, more pronounced in peripheral areas, consolidated density increases and reported viral pandemic in radiological terms . The patient was admitted to the COVID isolation clinic and began oseltamivir 2x75 mm oral, hydroxychloroquine 2x400 mg loading dose oral, azithromycin 1x500 mg oral, enoxaparin sodium 6000 anti-xa IU/ml 2x1 subcutaneous (sc) dose. On the 5th day of treatment, the patient was given 8 L/min O_2 support through a mask when SpO2 was <90% and favipiravir 2x1600 mg loading dose was begun due to accompanying severe pneumonia. With oseltamivir, hydroxychloroquine and azithromycin treatment stopped on the 5th day, the patient's COVID PCR test was positive. Due to high procalcitonin and CPR, empirical piperacillin-tazobactam 3x4.5 g intravenous (iv) was begun. On the 2nd day of this treatment, fever increased to 39.1 °C and prednisolone 2x40 mg iv was added to treatment. In spite of treatment on the 10th day of admission, the patient's blood gas SpO2 was <86% with 15 L/min O_2 support with a reservoir mask and with diagnosis of tachypnea, he was consulted with our clinic and admitted to the IC unit. Thoracic CT taken before admission to intensive care observed severe progression (Picture 1).



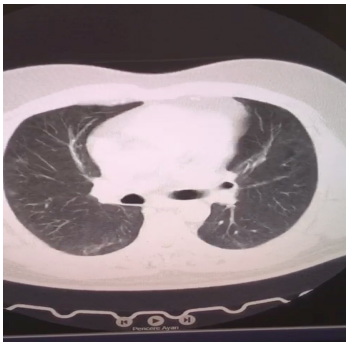
Picture 1

Thoracic CT taken on first admission to hospital. Both lungs have scattered and mainly peripheral nodular ground glass areas compatible with COVID-19 neumonia.

On the first day of intensive care admission, the patient had non-invasive mechanical ventilation (NIMV) support in CPAP/PS mode with FiO_2: 0.75 PEEP: 8 cmH_2O PEEP over: 12 cmH_2O treatment begun and respiratory rate (RR) was 40/min and SpO2 was 85%. After consultation with infectious diseases, tocilizumab 1x600 mg iv was added to treatment. On the 2nd day of admission, dipyridamole 2x75 mg oral was begun in addition to enoxaparin sodium 6000 anti-xa IU/mL 2x1 treatment.

On the 3rd day in intensive care, in addition to the previously-mentioned treatments, high flow nasal cannula (HFNC) began. A 2nd dose of tocilizumab 600 mg iv was administered. Thoracic CT taken on the 6th day in intensive care showed progression . The patient was monitored with spontaneous respiration using NIMV, HFCN and prone positioning until the 14th day of intensive care admission. From the day of IC admission, the patient had 30 μgr/ml 250 cc daily 1x1 OT with rectal insufflation. With stable and good general status, open cooperative consciousness, oriented and RR: 20/min, the patient was monitored under HFNC with FiO_2: 0.4 and 40 L/min flow. When BP: 100/85 mmHg, PHR: 85/min, and SpO_2: 95% NIMV values were present, NIMV treatment was stopped and one day later he was transferred from the IC to the post-COVID ward. In the ward, he was monitored with nasal oxygen, with occasional HFNC to keep SpO_2 >90%. On the 5th day in the ward, with the reduction in O_2 requirements and amelioration of clinical status, control thoracic CT was taken. With identification of findings in favor of PF, the patient had OT doses updated and continued with 30 μgr/ml 250 cc rectal insufflation twice per day and 25 μgr/ml 5 cc minor autohemotherapy method once per day. Receiving OT for 20 days, the patient was identified to have FiO2: 0.21 with SpO_2 99% under spontaneous respiration. With no requirements for O_2 support, the patient was discharged home; however, he attended our traditional complementary medicine (GETAT) center for 3 months to monitor and treat thoracic CT findings and was administered OT once per week. The patient was monitored closely in terms of PF on thoracic CT which was identified during intensive care and post-COVID clinic admission and treatment was organized. Ten days after OT doses were updated, the patient's oxygenation resolved and thoracic CT findings presented a risk for PF. For this reason, he was not discharged until 20 days and monitoring and treatment continued in the post-COVID ward. CTs were taken in both intensive care and the ward.

During follow-up with OT administration in the GETAT center, the patient's clinical status improved, effort dyspnea reduced and quality of life increased. Control thoracic CT taken in the 3rd month of follow-up observed close to full regression. Imaging in the 6th month after discharge observed full regression (Picture 2). The patient stated he could comfortably climb 4 flights of stairs and that complaints had fully resolved.



Picture 2

Control CT in 6th month after discharge. Full amelioration observed.

DISCUSSION

Among different possible treatments for SARS-CoV-2 pneumonia, OT appears to have an immunologic role due to modulation of cytokines and interferons including gamma interferon induction. Systemic OT controls inflammation, stimulates immunity and provides antiviral benefits. As a result, a new immune treatment method is encountered. Systemic OT for COVID-19 positive patients may create a synergic effect in combination with antiviral medications (14).

Ozone ensures pulmonary and peripheral tissue oxygenation and gas exchange via peripheral vasodilatation. Ozone modulates NRF2. This modulation contributes to improvement of normal functioning of inflamed tissues and reducing the amount of plasma interleukins. Ozone therapy may be chosen as a support treatment for COVID-19 treatment (15). In our case, clinical improvement beginning in IC was clearly observed in the first 10 days with ozone therapy in the post-COVID ward.

The sensitivity of thoracic CT for diagnosis of COVID-19 is very high, especially when assessed with serially taken CT images and 93% of reverse transcription-polymerase chain reaction (RT-PCR) negative patients have the chance for early diagnosis. Contact history, clinical findings and imaging findings are recommended as more sensitive for COVID-19 diagnosis of those with negative RT-PCR test (13).

Zheng et al. reported that OT could support improvement in clinical status and in thoracic CT images and shorten the viral transmission duration and hospitalization duration (16). In our cases, regression began to be observed on thoracic CT images taken during post-COVID ward monitoring from the 20th day of OT, clinical status fully resolved and the patient could be discharged without additional oxygen requirements.

We observed rapid regression in radiological findings with the improvement in oxygenation and rapid regression of respiratory distress in patients receiving OT especially in the post-COVID period in many of our cases, as in this case report.

Rowen R.J. et al. recommended the use of ozone for coronavirus treatment (8). Prospective cohort studies by Hernandez et al. reported the clinical improvement duration was significantly shortened with OT administered as autohemotherapy (17). In our case, pronounced clinical and radiological amelioration was identified within 20 days with only ozone treatment in the post-COVD ward.

Martínez-Sánchez et al. emphasized the effect mechanism of ozone involved reduction of IL-6 and IL-1 through immune modulation of the Keap1/Nrf2/ARE pathways (7). The principles and effect mechanisms underlying the cytoprotective activity of ozone therapy were proven clinically for other viruses and for this reason, it was emphasized that there was great need for clinical studies in the future to confirm potential use of ozone therapy for COVID-19 treatment.

The mechanisms causing fibroproliferation in acute respiratory distress syndrome and characteristic changes related to pulmonary injury develop over time and may be affected by a variety of environmental and patient-specific factors. In

response to alveolar-capillary injury, a temporary extracellular matrix (ECM) is created to support final repair and protein-rich pulmonary edema fluid is cleared from the alveolar cavity. Temporary ECM resolves after restoration of the majority of the pulmonary structure; however, in some patient groups the temporary ECM does not disappear and continuting fibroproliferation may occur months or years after acute events (13).

According to studies, ozone therapy has a protective role against ischemia-reperfusion injury by increasing the antioxidant activity in the redox balance. OT may be a potential source to modulate the patient's immune response to SARS-CoV-2. It may contribute to controlling cellular oxidative stress in COVID-19 pneumonia and breaking the negative feedback cycle of the cytokine storm in severe forms of the disease. OT may be a beneficial complementary treatment that should be noted to prevent progression to life-threatening disease in patients suffering from early-stage COVID-19 pneumonia (18,19).

CONCLUSION

Our clinic administers OT in preventive and treatment protocols to patients monitored with COVID-19 diagnosis and health personnel and it provides great benefit for treatment of post-COVID symptoms, as in this case. The efficacy of this treatment is observed in our clinic, continuing many prospective and retrospective studies related to OT. We predict OT will play an important role as effective and complementary treatment in both the disease and post-COVID periods during the COVID-19 pandemic.

REFERENCES

1. Conti P, Gallenga CE, Tetè G, Caraffa A, Ronconi G, Younes A, Toniato E, Ross R, Kritas SK. How to reduce the likelihood of coronavirus-19 (CoV-19 or SARS-CoV-2) infection and lung inflammation mediated by IL-1. J Biol Regul Homeost Agents. 2020 March-April,;34(2):333-338.

2. Li H, Du S, Yang L, et al. Rapid pulmonary fibrosis induced by acute lung injury via a lipopolysaccharide three-hit regimen. Innate Immun 2009; 15(3):143-54.

3. Hernández A, Papadakos PJ, Torres A, González DA, Vives M, Ferrando C, Baeza J. Two known therapies could be useful as adjuvant therapy in critical patients infected by COVID-19. Rev Esp Anestesiol Reanim. 2020 May;67(5):245-252. English, Spanish.

4. Schwartz A, Martínez-Sánchez G, de Lucía AM, Viana SM, Constanta AM. Complementary application of the ozonized saline solution in mild and severe patients with pneumonia COVID-19: A non-randomized pilot study. J Pharm Pharmacogn Res 2021; 9(2): 126–142.

5. Sunnen, Gérard V. "Ozone in medicine: overview and future directions." J Adv Med 1.3 (1988):15974.

6. Gavazza A, Marchegiani A, Rossi G, et al. Ozone Therapy as a Possible Option in COVID-19 Management. Front Public Health. 2020;8:417.

7. Martínez-Sánchez G, Schwartz A, Donna VD. Potential Cytoprotective Activity of Ozone Therapy in SARS-CoV-2/COVID-19. Antioxidants (Basel). 2020 May 6;9(5):389.

8. Rowen RJ, Robins H (2020) A Plausible "Penny" Costing Effective Treatment for Corona Virus - Ozone Therapy. J Infect Dis Epidemiol 6:113.

9. Wang, Z., Zhang, A., Meng, W., Wang, T., Li, D., Liu, Z., Liu, H., 2018. Ozone protects the rat lung from ischemia-reperfusion injury by attenuating NLRP3-mediated inflammation, enhancing Nrf2 antioxidant activity and inhibiting apoptosis. Eur. J. Pharmacol. 15 (835), 82–93.

10. Di Mauro R, Cantarella G, Bernardini R, et al. The Biochemical and Pharmacological Properties of Ozone: The Smell of Protection in Acute and Chronic Diseases. Int J Mol Sci. 2019;20(3):634.

11. Spagnolo P, Balestro E, Aliberti S. Pulmonary fibrosis secondary to COVID-19: a call to arms? Lancet Respir Med. 2020 doi: 10.1016/S2213-2600(20)30222-8. published online May 15.

12. Grillo F, Barisione E, Ball L, Mastracci L, Fiocca R. Lung fibrosis: an undervalued finding in COVID-19 pathological series [published online ahead of print, 2020 Jul 28]. Lancet Infect Dis. 2020;S1473-3099(20)30582-X. doi:10.1016/S1473-3099(20)30582-X

13. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv Wet al. Correlation of Chest CT and RT-PCR Testing for Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. Radiology. 2020;296(2):E32-E40.

14. Cattel F, Giordano S, Bertiond C, Lupia T, Corcione S, Scaldaferri M, Angelone L, De Rosa FG. Ozone therapy in COVID-19: A narrative review. Virus Res. 2021 Jan 2;291:198207.

15. Baeza-Noci J, Re L, Menendez, S. COVID19 and ozone therapy (ver 2.6) [Internet]. Brescia: WFOT; 2020 Apr 1 [cited 2021 Apr 10]. 5p. Available from: https://www.wfoot.org/wp-content/uploads/2020/04/OTCoV22F.pdf

16. Zheng Z, Dong M, Hu K. A preliminary evaluation on the efficacy of ozone therapy in the treatment of COVID-19. J Med Virol. 2020;92(11):2348-2350.

17. Hernandez A., Viñals M., Pablos A., Vilas F., Papadakos P., Wijeysundera D., Vives M. Ozone therapy for patients with SARS-COV-2 pneumonia: a single-center prospective cohort study medRxiv 2020.06.03.20117994; doi: https://doi.org/10.1101/2020.06.03.20117994

18. Izadi M, Cegolon L, Javanbakht M, Sarafzadeh A, Abolghasemi H, Alishiri G, Zhao S, Einollahi B, Kashaki M, Jonaidi-Jafari N, Asadi M, Jafari R, Fathi S, Nikoueinejad H, Ebrahimi M, Imanizadeh S, Ghazale AH. Ozone therapy for the treatment of COVID-19 pneumonia: A scoping review. Int Immunopharmacol. 2020 Dec 21;92:107307.

19.Tascini C, Sermann G, Pagotto A, Sozio E, De Carlo C, Giacinta A, Sbrana F, Ripoli A, Castaldo N, Merelli M, Cadeo B, Macor C, De Monte A. Blood ozonization in patients with mild to moderate COVID-19 pneumonia: a single centre experience. Intern Emerg Med. 2020 Nov 1:1–7.