



COVID19 and ozone therapy (ver 2.6)

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1.- INTRODUCTION.

SARS-Cov2, virus causing COVID19 disease, has a mean incubation period of 5 days, although it can reach up to 2 weeks¹.

Infected patients evolve differently and extreme cases have fatal outcome after 10 days of being infected. Most patients ask for medical help after 5 days of suffering a cuff-fever syndrome that worsens. They usually remain in-hospital for 3 weeks before discharge but according to age and concomitant pathology, 10-15% go to ICU. The prognosis there is also related with age and concomitant diseases as indicated by WHO².

1.1. Ozone therapy possible role in COVID-19.

Bocci and cols.³ tested *in vivo* effects of ozone in patients with different diseases and discovered the following facts:

1- Ozone **improves lung and peripheral tissue oxygenation** and exchange of gases, because of peripheral vase-dilatation mediated by nitrosotyols and enhanced glucolysis in erythrocytes that produce more ATP and secondary higher 2,3-DPG levels (Bohr effect) and more elasticity because an optimal functioning of Na/K⁺ membrane pump².

2- Ozone modulates NRF2⁴ and this produces three effects. First⁵, normalize the redox balance through the increase in antioxidants in cytoplasm, mitochondria and finally, plasma, mainly glutathione peroxidase, but also glutathione reductase, NADPH and SOD. Second⁶, induces the production of HO-1, a protective enzyme, together heat-shock proteins like HSP60, HSP70 and HSP90. Third⁷, modulates NFKbeta that **regulates the production of pro-inflammatory interleukines** in inflammated tissues. All three effects contribute to restore the normal functioning of the inflammated tissues and decrease the amount of plasma interleukines.

Many **pre-clinical** papers⁴ have confirmed these results, but there are also **clinical studies** that have confirmed these facts:

- Hernandez-Rosales and cols.⁸ in 2005 reported the **improvement of asthma patients** in both, analytical tests and respiratory function after ozone systemic treatment and also compared the effect of different doses of ozone.

- Calunga and cols.⁹ in 2011 got the same results in patients suffering from **emphysema**.

- Borrelli and Bocci¹⁰ in 2014 confirmed these results in other group of **chronic obstructive pulmonary disease (COPD) patients**.

- Vinnik and cols.¹¹ proved in 2015 the **decrease in IL6 and other pro-inflammatory citokynes in diabetes mellitus patients** treated with systemic ozone.

- Delgado-Roche and cols.¹² also published in 2017 the **same findings in multiple sclerosis patients**.

- Tong and cols.¹³ published in 2018 a **great decrease in IL6 in patients suffering lumbar disc herniation** and treated with systemic ozone.

Many papers⁴ have been published about the improvement of bacterial infection by using systemic ozone. Bocci also proposed the rationale of this indication^{14,15}. Fortunately, we have several **clinical studies** about the efficacy of ozone in viral infections: herpes^{16,17,18,19} hepatitis B^{20,21,22,23}, hepatitis C^{24,25}, HPV²⁶ and HIV²⁷.



1.2. Ozone administration ways.

Ozone for systemic diseases should be used in a systemic way¹:

A. Indirect Endovenous Administration (IEV). Special medical devices have been manufactured and EU certificated by different manufacturers to allow ozone dissolve into the patients' blood risk free. For details on this technique, please read World Federation of Ozone Therapy - WFOT's book².

Based on the information from the three Chinese Hospitals^{28,29,30} that are presently performing an official clinical trial and also on the protocol presented and pre-accepted in Università della Sapienza in Rome, the proposed treatment will be:

- 100 mL of blood and 100 mL of ozone gas at 30 mcgr/mL concentration.
- In-hospital patients: each 12 hours application for minimum 14 days.

B. Rectal Insufflation (RI). Rectal insufflation is not so exact as IEV but it can be the only option for patients where peripheral veins don't allow the previous technique. For details on this technique, please read World Federation of Ozone Therapy - WFOT's book².

We propose the following protocol:

- Day 1: 100 mL at 30-40 mcgr/mL concentration.
- Day 2: 150 mL at 30-40 mcgr/mL concentration.
- Day 3 - 14: 200 mL at 30-40 mcgr/mL concentration.
- In-hospital patients: each 12 hours application for minimum 14 days.

1.3. Complementary treatments to ozone administration. (OPTIONAL)

To help ozone effect, it is possible although not mandatory, the administration during the ozone treatment of:

- Vitamine C: 3 gr each 12 hours, 6 hours after ozone administration. 1 gr each 12 hours is already standardize in Italy and Spain protocols for COVID19.
- Glutathione: 600mg each 12 hours, 6 hours after ozone administration. This substance is administered because ozone effect is partially based on it and old patients may have a low blood glutathione level.

2. TRIAL DESIGN.

2.1. Purpose:

1. Enhance respiratory function.
2. Stop the blood interleukine storm.
3. Limit patients needing ICU.
4. Shorten the time in hospital.

2.2. Inclusion criteria:

1. Confirmed patients (or legal guardian) sign a written informed consent form.
2. Aged from 18 to 80 years, male or female.
3. Patients with positive detection of 2019 Novel Coronavirus Pneumonia fluorescence RT-PCR in respiratory specimens or blood samples.
4. Mild ill and severe ill patients NOT IN ICU are grouped based on the "Handbook of COVID-19 Prevention and Treatment"³¹.

2.2. Exclusion criteria:

1. Patients who may be transferred to other hospitals that are not included in the trial within 72 hours.
2. G-6PD defect (Major Favism).
3. Pregnancy, especially early pregnancy.
4. Patients who continually use immunosuppressant, or are organ transplant recipients within 6 months.
5. Patients who are receiving other clinical trials.

2.3. Interventions:

WE PROPOSE RANDOMIZING the patients going for control, IEV or RI groups:

1. Control group. 60 patients. Conventional treatment.
2. Mild ill patients: 15 patients. Conventional treatment + ozone protocol A (IEV).
3. Mild ill patients: 15 patients. Conventional treatment + ozone protocol B (RI).
4. Severe patients: 15 patients. Conventional treatment + ozone protocol A.
5. Severe patients: 15 patients. Conventional treatment + ozone protocol B.

2.4. Outcomes:

1. Primary:
 1. Chest CT or XRay: interstitial pattern.
 2. Whole blood cell analysis: leucocytes recount.
 3. Oxygenation index: SpO₂.
 4. Inflammation index: PCR, IL6. (optional: IL2, procalcitonin, ferritin, D-dimer)
 5. Fever: axillary temperature.
2. Secondary:
 6. Recovery rate.
 7. Conversion rate of severe patients.
 8. Mortality rate.

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