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Theoretical Basements for a Clinical Trial on COVID-19 Patients with Systemic Ozone Therapy

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Abstract

Systemic ozone treatment has proved, in different clinical studies, to enhance exchange of gases and blood circulation, improve lung function in chronic pulmonary diseases, reduce viral load in patients infected by Herpes virus, Hepatitis B and C virus, Human Immunodeficiency virus and reduce significantly IL-6 and other proinflammatory cytokines in chronic inflammation diseases. All these results support the rationale to set up a clinical trial for patients suffering COVID-19 as an adjuvant treatment until we found an eventual cure.

Keywords: *COVID-19, Ozone therapy, SARSCoV2, Systemic ozone treatment*

Proposed Hypothesis

Due to the extreme world situation caused by COVID19 pandemic we consider unethic not to try any treatment option with a justified rationale. We have explained that medical ozone therapy has a clear scientific basement thanks to all preclinical investigation already published. It can be classified as chemical stressor that produces a modulation of the redox balance and immunity. Moreover, it is easy and safe to administer [1]. The efficacy in viral diseases have been published together the modulation of IL-6 and other proinflammatory cytokines that could potentially help in COVID19 patients. We proposed to carry out a randomized control trial to evaluate the safety and efficacy of systemic ozone (indirect endovenous and rectal) in these patients.

Introduction

Coronavirus

The new Severe Acute Respiratory Syndrome (SARS) produced by the new coronavirus, SarsCoV2, has been expanding since past December and declared by WHO as pandemic. Today (March, 27th, 2020) there are 465915 confirmed patients and in Spain the number of cases is 65719 [2]. Mortality rate is around 3.7% and there is no proved treatment [3]. From a clinical point of view, it produces an acute respiratory distress with hemophagocytic lymphohystiocytosis that induces a fatal increase of blood cytokines. The patients also show increased ferritin, interleukyne 6 (IL-) and decrease of platelets as markers of a starting huge inflammation process that can lead to heart failure [4]. In severe ill patients, we found increased prothrombin time, partial thromboplastin time, D-dimer, lactate-dehydrogenase, procalcitonine, albumin, C-reactive protein and aspartate aminotransferase [5].

Medical Ozone Therapy

Medical ozone is a mixture of ozone and medical oxygen produced by a trustable and accurate medical device. Ozone therapy is the use of medical ozone, a safe therapeutic agent, to treat pain and other diseases. Due to the growing interest on these techniques, the World Federation of Ozone Therapy - WFOT published in 2015 a scientific review devoted to health professionals interested in knowing and understanding the biochemistry, pharmacology and indications of medical ozone [6].

Ozone Germicidal Effect

Ozone has proved its efficacy against virus, bacteria (gram positive as well as gram negative), fungus and spores. This is due to its high oxidant capacity that cannot be handled by the classical microbial resistance mechanisms and damages the microbial membranes irretrievably [7]. Its effect is universal but selective. Universal, because it is effective in all microbes, even for Pseudomonas aeruginosa and Escherichia coli, both with a high antibiotic resistance. Selective, because it respects eukaryot healthy cells, due to the huge antioxidant capability of them and their environment. We can find papers about this effect on MS2 bacteriophage virus, Norwalk Virus, poliovirus 1, hepatitis A and Coxsackievirus [8-11].

The inner mechanism of germicidal effect is due to:

- Double bounds in polyunsaturated fatty acids (PUFA) of the membrane being broken by ozone.
- Amino acids (cysteine, methioine, histidine) reacting with ozone in their thiols groups.

Over viruses, apart from the membrane damage, lipid peroxides from the membrane reaction interfere the reverse transcriptase, basic for the virus replication [12]. This antimicrobial effect has nothing to do with the in vivo mechanisms of action that contribute to the infection cure and that could be useful for COVID-19 patients.

Biological Effects of Medical Ozone

The administration of medical ozone in order to protect and repair organic damage has demonstrated to be an effective and safer stress than the ischemic one. Ozone has proved to be effective against hepatic damage induced by ischemia/reperfusion [13-17], partial hepatectomy [18] or toxicity by carbon tetrachloride [19] or methotrexate [20]. It has also been proved that ozone enhances the ketamine hepatoprotection in septic rats [21]. Similar findings have been reported for renal damage in ischemia/reperfusion models [22-28], toxicity due to radiological contrast [29], adriamicine [30], partial nephrectomy [31], diabetes [32] or methotrexate [33].

Also, in heart and skeletal muscle damage due to ischemia/reperfusion or toxicity by doxorubicin [34-38]. Intestinal damage induced by methotrexate [39], lung irradiation damage [40], fecal peritonitis [41] and endotoxic shock [42]. From these papers about ozone oxidative preconditioning, we know the biological mechanisms underneath the tissue restoration induced by the ozone mild controlled oxidative process. The biochemical reaction of medical ozone on the PUFA transported by albumin generates (Criegee's reaction) alpha-hydroxy-hydroperoxydes, hydrogen peroxide, and aldehydes, like 4-hydroxynonenal. These last are well known signaling molecules modulating inflammation, proliferation, growing and cellular death (necrotic or apoptotic) [43,44].

The mild acute oxidative stress induced by ozone also modulates the activation of different nuclear transcription factors (NF) [45]: Nuclear Factor of Activated T-cells and Activated Protein-1, Goth related with immunity, Hypoxia Inducible Factor-1a, related with vascular degeneration and NRF2 (Nuclear factor Erythroid-2-Related Factor-2), that regulates the synthesis of mediators of inflammation and antioxidant enzymes (SOD, GPx, GSTr, CAT, HO-1, NQO-1, NADPH). Also modulates the release of heat shock proteins (HSP) that have a protective effect [46] especially in oncological [47,48] and infectious diseases [49]. Pecorelli and Bocci checked an increase of NRF2 in plasma from healthy volunteers after ozone administration to cell cultures. The increase was dose related with a positive increase as ozone dose increased from 20 to 80 μg/mL [50,51]. Similar results were published by Re and cols. that also observed an increase in several heat shock proteins: HSP-60, HSP-70 y HSP-90 [52]. Related with this NRF2 modulation, a decrease in proinflammatory cytokines in multiple sclerosis patients has been published [53].

In erythrocytes, mainly through hydrogen peroxide that accelerates intra erythrocytes glycolysis and so, produces more ATP and an increase of 2, 3-DPG, two changes are induced that help to improve blood circulation:

1. The increase of 2, 3-DPG produces a shift to the right in the oxygen/hemoglobin dissociation's curve (Bohr effect) [54]. There is an increase in the exchange of gases in lungs and peripheral tissues because of this.
2. Improvement of the Na/K2+ membrane pump, ATP dependent, that restores the membrane function usually affected in chronic illness [55]. This effect improves the blood rheology and microcirculation.

Moreover, ozone lipid peroxides induce the release of endothelial nitric oxide and nitrosotyhyols [56] that induce local and remote vase dilatation, antithrombosis and regulation of heart contractility [57,58].

All these effects produce a great improvement of peripheral tissues oxygenation [59].

Clinical Studies

Clinical applications of medical ozone started at the beginning of the last century. In 1911 Dr. Noble Eberhart, chief of the department of physiology in University of Loyola (Chicago, Illinois, USA) published the book "A Working Manual of High Frequency Currents" that promotes the use of medical ozone for TBC, anemia, asthma, bronchitis, diabetes and others [60]. Today, in PubMed we can find more than 3000 papers on ozone therapy and more than 1200 are clinical studies [61]. Medical ozone therapy is used in Pain Medicine since 80s [62,63] having presently the highest level of evidence for specific indications; also, some dental applications have also a high level of evidence, mainly due the germicidal effect already commented.

Cardio and Cerebrovascular Diseases

The generic improvement of the blood circulation caused by medical ozone and the specific effect on the atheromatous plaque will be especially useful for this kind of diseases [64-66]. Giunta and cols. checked that 27 patients suffering of peripheral occlusive arterial disease treated with systemic medical ozone improved, not also the antioxidant capability but also the blood's perfusion and viscosity, hematocrit and fibrinogen, with no side effect [67]. A Cuban study recruited 120 patients with risks factors for heart attack and randomized them in 2 groups: control and treatment (ozone rectal insufflation). During one year, each 3 months, several clinical and biochemical parameters were registered. Ozone group was quite more stable both clinical and biologically. No side effects were found [68]. Other Cuban team treated 22 patients post heart attack with systemic indirect endovenous ozone application daily for 3 weeks and showed an improvement in the lipid metabolism and antioxidant capability. No side effects were detected [69]. The same team treated 120 patients with acute, subacute and chronic cerebrovascular disease. After 20 applications of rectal ozone, 86% of the patients improved clinically, specially the acute ones [70].

Neumology

A published clinical trial proved the efficacy of systemic ozone at different doses and ways of administrations in asthmatic patients. Improved in Ig E and antioxidant status together a decrease in

inflammation markers. Indirect endovenous ozone was more effective at the same dose [71]. These findings were also found in a group of patients with emphysema treated with 2 cycles of 20 applications of rectal ozone insufflation. They found no side effect [72]. Borrelli and Bocci randomized 50 patients suffering chronic obstructive pulmonay disease in 2 groups: control and treatment with systemic indirect endovenous ozone. There found no improvement in basal oxygenation or lung function but they found improvement in effort tests: 6MWT, Borg dyspnoea scale, SGRQ, concentration and memory capability. No side effects were observed [73].

Immunomodulation

In 1990, Bocci and Paulesu studied the in vitro effects of ozone on human blood's leukocytes in concentrations from 2.2 and 108 mcg/mL for 30 seconds. These authors found that concentrations around 42 mcg/mL were optimal for increasing interferon [74]. Years later, another in vitro studies showed that 40mcg/mL produced optimal modulation on NFKβ and pro inflammatory cytokines without any side effect [75,76]. Primary IgA deficiency patients found more improvement with systemic ozone that with Transfer Factor 1 [77]. In secondary immunodeficiency pediatric patients treated with systemic ozone also improved clinically with a decrease in the infection rate and without side effects [78].

Chronic Inflammation and Autoimmune Diseases

Medical ozone has shown efficacy and safety in the treatment of chronic inflammatory intestinal diseases [79,80] and rheumatoid arthritis [81,82]. All parameters improved in the groups treated also with systemic ozone.

Clinical trials have validated a decrease in IL-6 and other proinflammatory cytokines in diabetes mellitus [83], multiple sclerosis [53] and lumbar disc herniation patients [84]. This decrease was correlated with a clinical improvement and a stabilization in the course of the diseases.

Viral Infections

Herpes Virus. Medical ozone has found to be effective for herpes virus through local injections, topical ozonized oil and water and also in systemic administration. In postherpetic neuralgia, clinical enhancement has been detected through clinical studies with control groups using injected ozone around the dorsal root ganglium alone [85], combined with pregabaline [86] or with retrovirals and acupuncture [87] and epidural injected [88]. Also, ozone injections have been tested with and without pulsed radiofrequency showing the superiority of combining both treatments [89]. Trigeminal postherpetic neuralgia also improved with local injections of ozone around Gasser ganglium [90]. In mouth pathology, ozonized oil has found to be useful for cold sores [91]. Other studies have been published about topical ozonized oil and water in cutaneous herpetic neuralgia with positive results [92,93].

Systemic ozone has proved to reduce significantly viral load in Herpes 1, 2 and Citomegalovirus [94]. Other controlled trials showed improvement not only for viral load but also for pain and quality of life. No side effects were found [95].

HIV. Based on in vitro preclinical studies [96] some authors have proposed and tried the efficacy and safety of systemic ozone in HIV. Bocci tested indirect endovenous approach [97] in 12 patients; after 7 months with 50 applications for patient and no side effect, he found no change in viral load [98]. Garber did 2 clinical studies (phase I and II) using indirect endovenous ozone in 10 HIV patients. Ozone therapy was well tolerated but did not improve either any analytic parameter; although some clinical improvement was found for concomitant pathologies [99]. We want to mention Carpendale publication that obtained good results in reducing the diarrhea of these patients with rectal ozone insufflations [100]. Recently, Cespedes and cols. have published good results with a significant decrease of viral load and increase in CD4 and CD8 in 32 patients with 15 applications of systemic indirect endovenous ozone. No side effects were reported and quality of life improved [101].

Viral Hepatitis. Both, systemic indirect endovenous or rectal insufflation application of ozone have found to be effective. In 2009, Neronov published his experience on chronic B hepatitis. He concluded that there was an improvement in clinical and biochemical parameters and a decrease in gallstone rate [102]. These results were confirmed later by Chemishev [103]. A randomized control trial was published in 2008 treating 40 hepatitis B patients with conventional treatment and 20 of them also with systemic endovenous ozone. The improvement was significantly greater in the ozone group [104]. Last study on hepatitis B showed that 28 patients with clinical stability under retroviral treatments were submitted for systemic indirect endovenous ozone treatment. After 15 applications, HBs Ag and viral load decreased [105]. For hepatitis C, a similar study was done founding a greater decrease in ALT, AST and viral load; the decrease was proportional to the number of applications [106].

Gu and cols studied patients with severe chronic hepatitis C and renal failure. The randomized trial showed an improvement in liver and renal function with also an increase survival rate in the systemic ozone group [107].

Safety of Medical Ozone Therapy

Medical ozone therapy, properly applied, has been found safe thanks to all preclinical toxicological test performed according to Food and Drug Administration (FDA), World Health Organization and Cuban Regulatory Agency rules [108]. Acute and chronic toxicological tests have been carried out for rectal and intraperitoneal administrations. No adverse reaction was related to ozone. For rectal insufflation, also irritation test was performed with no side effect registered neither in acute or chronic administration.

The safety of ozone on blood was thoroughly studied by Bocci and cols [57]. Moreover, no adverse reaction was found for mutagenic, carcinogenic and teratogenic tests, in vitro and in vivo. However, ozone breathing was found to be extremely toxic, due to the minimal antioxidant capability of the alveolar fluid [109].

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