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COVID-19: POTENTIAL FOR HEMOTHERAPY WITH OZONE THERAPY OF PATIENTS AFTER ACUTE CIRCULATORY DISORDERS

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Abstract:

SARS-CoV-2, the cause of COVID-19, is the newest member of the Coronaviridae family of viruses and is the third coronavirus crossing animal species barriers to infect human populations. Systemic ozone therapy can be potentially useful in SARS-CoV-2. The rationale and mechanism of action has already been proven clinically with other viral infections similar to SARS-CoV-2. Here we report the history of ozone therapy, its activity against infectious agents, and techniques which are likely to be the most efficient in culling the massive virion waves that viremic episodes spawn. Ozone is reported to activate the immune system in infectious diseases to improve the utilization of oxygen and stimulate release of growth factors and other mediators that may re-activate the immune system and reduce ischemia in vascular disease, now known to be a significant contributor to adverse Covid-19 outcomes. Ozone therapy may be an important adjuvant to more conventional therapies such as vaccines in severe infectious disease and pandemics including that caused by SARS- CoV-2.

Keywords: ozone therapy, innate immune system augmentation, adaptive immune system augmentation, vaccine adjuvant, sars-cov-2, covid-19 treatment support.

Introduction :

Covid-19 is the newest member of the Coronaviridae family of viruses and is the third coronavirus crossing animal species barriers to infect human populations. The previous two members of the family are the severe acute respiratory syndrome coronavirus (SARS-CoV), emerging in 2002, and the Middle East respiratory syndrome coronavirus (MERS-CoV), in 2012. All can cause severe, even fatal, sudden acute respiratory syndrome or severe cardiopulmonary distress. The SARS-CoV-2 may also be creating a systemic hypoxic environment by inhibiting the functioning of Heme.

Covid-19 attests to the high mutational capacities of Coronavirus family members. By extending their reservoir range to include other animal species (such as pangolins), by delaying the onset of symptoms while maintaining infectivity, and by further mastering human-to-human transmission

and expanding vectoring routes to include droplet, oral-fecal, and body fluids modes (Zhang et al., 2020), SARS viruses greatly expand their capacity to create epidemics and pandemics.

As with many viruses, coronaviruses have complex host invasion, replication, and transmission cycles. A crucial replication phase, known as the viremic phase, involves the explosive reproduction of viral particles and virions, exiting from infected and dying host cells, disgorging billions of viral progenies, daily, into many types of bodily fluids. Indeed, in these massive seedlings, all organs are suddenly virally overwhelmed and existentially challenged, leading to a cytokine storm and sepsis.

The present thesis proposes a low-cost and potentially highly effective method for reducing coronavirus blood stream onslaughts, Extracorporeal Blood Oxygenation-Ozonation (EHO). Bona fide COVID-19 pharmaceuticals are not proven, and the human immune response is too often incapable of abating since normal T-cell activation is known to be sluggish due to the body‘s naiveté relative to novel SARS antigens. This results in delayed response times and often severe or fatal disease. Reduction of viral load, through ozone treatment, is posited to offer a plausible emergency viral abatement strategy. This approach may also be applied in prevention for asymptomatic but virus positive individuals, amelioration of disease severity, or curing current disease in non-emergency settings.

Coronavirus, Genome and Classification :

Coronaviruses (CoV) are a member of a diverse group of RNA viruses comprised of a large genome size varying between 26 to 32 kb. They are named for the crown-like (or corona in Latin) spikes of the virus protruding to the periphery with a diameter of 60-160nm under electron microscopy. The largest group of CoVs belong to the Nidovirales order, which contains Coronaviridae, Arteriviridae, and Roniviridae families known to induce common colds and diarrheal illnesses in humans (Chen et al., 2020). The viral genome is linear and monopartite with a positive sense ssRNA genome. The linear RNA genome of CoVs is capped and polyadenylated. The 5‘ end of the CoV genome encodes replicase gene which contains two large open reading frames (ORFs), ORF1a and ORF1b. They encompass around two-third or ~20 kb of the genome. Replicase gene translates two large polyproteins, pp1a and pp1ab. The polyprotein pp1ab is expressed as a result of the translational frameshift between ORF1a and ORF1ab. The replicase polyproteins are further cleaved into 16 proteins which include proteins related to enzymatic activities, protease activities, polymerases and helicases which fuses with a zinc finger complex at the N-terminus and a Zn-ribbon-containing papain-like proteinase (Malik et al., 2020). The recent 2019-nCoV or SARS-CoV-2 is a member of genus Betacoronavirus in the subgenus Sarbecovirus. The SARS-CoV and MERS-CoVs are quite distant at genomic levels to current 2019-nCoV but are part of the Betacoronavirus genus. The SARS-CoV-2 shows lower similarity (50-51.8%) with MERS-CoV and similarity is near to 79% with SARS-CoV (Malik et al., 2020). Transmission, Incubation, Clinical Manifestation, and Risk Stratification A study conducted by experts from the US Centers for Disease Control and Prevention (CDC), NIH, UCLA, and Princeton University investigated how long the virus remained infectious on different surfaces. The investigators found that SARS- CoV-2 is detectable in aerosols for up to 3 hours, on copper up to 4 hours, up to 24 hours on cardboard, and up to 3 days on plastic and stainless steel. —The results provide key information about the stability of SARS-CoV-2, which causes COVID-19 disease, and suggests that people may acquire the virus through the air and after touching contaminated objects, according to an NIH press release. The SARS-CoV-1 and 2 exhibit similar stability ex vivo, however the contagious period appears to significantly precede symptoms when SARS-CoV-2 as compared to SARS-CoV-1. (Liu et al., 2020b) estimated that the mean incubation period of infection with SARSCoV-2 was 5.2 days (95% CI, 4.1–7.0), with the majority of

the cases showing symptoms within 12.5 days of exposure, justify 14 days of quarantine. However, recent reports suggest that more than 14 days incubation period was observed in exposed persons recommending a double quarantine period of 28 days. Recent epidemiological analysis indicates that the exposed person may act as a source of infection to others during the incubation period. According to the WHO the estimated reproductive number (R0) to be 2.2 (95% CI, 1.4–3.9); however, have determined an R0 between 3.6 and 4.0, and between 2.24 to 3.58 and 7.4 days (95% CI, 4.2–14), respectively (Lu, Zhao & Li, 2020).

Major initial clinical symptoms of COVID-19 include fever, most of which are high fevers that occur within several days and are not alleviated by routine anti- infective drugs, additionally coughing, headache and muscle pain or fatigue (Liu et al., 2020a). Other clinical symptoms observed at low frequency include elevated troponin levels, diarrhea, myalgia and myocarditis. (Liu et al., 2020a) It should be emphasized that asymptomatic patients are also positive for 2019-nCoV (Chang et al., 2020), so the presence of asymptomatic carriers requires due attention, and potentially treatment to reduce transmission. Nearly 20% of the patients appeared comorbidities with regard to the dysfunction of other organs, primarily renal impairment and patients with underlying cardiovascular diseases often demonstrated comorbid heart failure. (Huang, Wang & Li, 2020) They gradually develop initial symptoms in the cardiovascular system, digestive system, and nervous system, which increased the difficulty of diagnosis (Liu et al., 2020a).

The COVID-19 may present with no, mild, moderate, or severe illness. Among the severe clinical manifestations, there are severe pneumonia, ARDS, sepsis, hypoxia, and septic shock. The clinical course of the disease seems to predict a favorable trend in the majority of patients. In a percentage still to be defined of cases, after about a week there is a sudden worsening of clinical conditions with rapidly worsening respiratory failure and MOD/MOF. As a reference, the criteria of the severity of respiratory insufficiency and the diagnostic criteria of sepsis and septic shock can be used (Kogan et al., 2019).

Serious cases can quickly progress to acute respiratory distress syndrome, septic shock, irreformable metabolic acidosis, coagulopathy and multiple organ failure. Nearly 80% of the patients have normal or decreased white blood cell counts, and 72.3% have lymphocytopenia (Liu et al., 2020a). Lung involvement was present in all cases (Liu et al., 2020b), with most chest computed tomography (CT) scans showing lesions in multiple lung lobes, some of which are dense. Ground-glass opacity co-existed with consolidation shadows or cord-like shadows are observed. Since respiratory supports are administered to most of the patients, oxygen saturation can be maintained at above 90% as indicated by pulse oximetry monitoring (Liu et al., 2020a). It is reported that severe and critically ill patients have moderate to low fever, even without obvious fever. Mild patients show just low fever, mild fatigue, and no pneumonia. Judging from the current cases, most patients have a good prognosis but poor for the elderly and those with chronic underlying disease. Symptoms in children are relatively mild.

SARS-CoV-2 may work to create tissue damage by multiple mechanisms. Virus surface open reading frame glycoproteins may bind to the porphyrin of heme. It is also reported that these proteins may attack the heme on the 1-beta chain of hemoglobin to dissociate the iron to form the porphyrin. Biochemical examination of 99 patients with novel coronavirus pneumonia also showed abnormal hemoglobin-related biochemical indexes (Chen et al., 2020). This report demonstrates that the hemoglobin and neutrophil counts of most patients have decreased, and the index values of serum ferritin, erythrocyte sedimentation rate, C-reactive protein, albumin, and lactate dehydrogenase of many patients increase significantly. This data implies that the patient's hemoglobin is decreasing,

and the heme is increasing, as the body accumulates too many oxidizing iron ions, which will cause inflammation in the body and increase C-reactive protein, albumin, and other markers of inflammation.

Quantitatively measuring physiological health is an important component in determining aspects of immunity involved in controlling viral replication. It is also crucial in identifying and staging sufferers when resources are consumed as in periods of pandemics. Initial serology indicates changes to the following markers, that are current used to risk stratify hospitalized patients at Mass General Hospital: CBC with diff (trend total lymphocyte count), Complete metabolic panel, CPK (creatine kinase), (Jin, Cai & Cheng, 2020), D-dimer, Ferritin, ns-CRP, ESR, LDH, Troponin, and baseline ECG. All patients in any must undergo a through medical workup when practical, for risk stratification, triage prioritization, and future screening for disease vulnerability (Mehta et al., 2020).

Ozone Therapy :

Medical ozone therapy is used to disinfect and has a 150-year history of successful use to treat infections, wounds and multiple diseases. It has been used to disinfect drinking water before the turn of the last century. Ozone was known to treat many inflammatory and infectious diseases (Shoemaker, 2010).

During the first world war (1914-1918) doctors familiar with O3's antibacterial properties, and with few other medical resources available to them applied it topically to infected wounds and discovered O3 not only remedied infection, but also had hemodynamic and anti-inflammatory properties (Stoker, 1902). In the late 1980s, reports had emerged that German physicians were successfully treating HIV patients with 03-AHT (Autohemotherapy) (Wells et al., 1991). Ozone in Treating Infectious Disease Ozone, because of its special, pathogen-agnostic, oxidative biological properties, has theoretical and practical attributes to make it a viable candidate as a Covid-19, MERS, and SARS viral load-culling agent. The key to this strategy is embodied in coronaviral vulnerability to oxidizing agents due to the fragility of their lipid-rich envelopes.

The technology of interfacing oxygen-ozone gas mixtures with bodily fluids has long been mastered (Viebahn, 2007; Bocci, 2013, Di Paolo, Gaggiotti & Galli, 2005; Smith et al., 2017) and finds support in the vast scientific literature dating back to the 19th century on the chemical, biochemical, immunological, and otherwise physiological oxidative effects of ozone on bodily systems. This mode of action is consistent with and likely augments the action of the innate immune system driven by the production of peroxide by white blood cells, the former that acts as a —first responder to injured tissue (Niethammer et al., 2009). A proposal is herewith made for the further study of parenteral administration of calibrated oxygen/ozone gaseous mixtures in the critical care of Covid-19, SARS, and MERS, with subsequent extension to mild and asymptomatic cases. We further propose to include a broad workup of each participant that includes Covid-19 risk stratification biomarkers used at Mass General Hospital to triage patients. Showing a relationship between known biomarker, ozone treatment, and disease symptoms may provide adequate evidence to advance this technology, if successful. Timing is crucial to demonstrate non-pharmaceutical solutions that can be distributed and administered widely in anticipation of new infections that will inevitably impact society. This can be achieved via a number of technologies that have long been the purview of pioneer physicians. Most experience has been gleaned from methods utilizing the serial treatment of blood aliquots with oxygen/ozone gaseous mixtures, known as autohemotherapy (AHT). More comprehensive methods—although more sophisticated but ones

that have greater potential to succeed in Covid-19 culling— involve the treatment of the total blood and lymph volumes via techniques called extracorporeal blood oxygenation ozonation—EHO (Di Paolo et al., 2002). Systemic ozone therapy can be potentially useful in SARS-CoV-2. The rationale and mechanism of action has already been proven clinically with other viral infections similar to SARS-CoV-2. The mechanism of action is as follows: 1) The induction of adaptation to oxidative stress, hence a re-equilibration of the cellular redox state. 2) The induction of IFN-gamma and proinflammatory cytokines. 3) The increase of blood flow and tissue oxygenation to vital organs (i.e. renal, pulmonary and cardiac circulation). 4) It has the potential to act as an auto-vaccine when administered in the form of minor Autohemotherapy (Elvis & Ekta, 2011).

Recently, there has been renewed interest in the potential of ozone for viral inactivation in vivo. It has long been established that ozone effectively works against the viability of bacteria, viruses, fungi, and parasites in aqueous media. Ozone- susceptible viruses include Adenoviridae, Filiviridae, Hepnaviridae, Herpesviridae, Orthomyxoviridae, Picornaviridae, Reoviridae, Retroviridae, and Coronaviridae (Viebahn, 2007; Sunnen, 2009; Bocci, 2013).

Some viruses are more susceptible to ozone‘s action than others. It has been found that lipid-enveloped viruses are the most sensitive. This makes intuitive sense, since enveloped viruses are designed to blend into the dynamically constant milieu of their mammalian hosts. This group includes hepatitis B and C, herpes 1 and 2, Cytomegalus (Epstein-Barr), HIV 1 and 2, influenza A and B, West Nile virus, Togaviridae, and Western equine encephalitis, rabies, and Filiviridae (Ebola, Marburg), among others. Prominent are all Coronaviridae family members, including Covid-19, SARS, and MERS.

Result :

4.1. Ozone in COVID-19 :

As of April 2, 2021, there are 17 hospitals using Scientific Society of Oxygen- Ozone Therapy (SIOOT) oxygen ozone therapy to treat people affected by COVID-19. From preliminary reports on autopsies of those who died from COVID-19, it appears that the virus immediately attacks the microcirculation system causing widespread thrombosis. Several hospitals are using Major AutoHemo Therapy (MAHT), a protocol that extracts the patient's blood, bubbles oxygen ozone through the blood in a saline or heparin bag and is infused back into the patient. Patients showed clinical improvement in 1-2 days of receiving one infusion, one time a day.

Case 1:

AD is a 37-year-old female who presented on April 15, 2020 with twoday-old complaints of fever (temperature fluctuating between 100-102 degrees Fahrenheit), cough, loss of sense of taste and smell, gastrointestinal disturbances including two episodes of diarrhea and having an upset stomach, body aches, and shaking as well as severe fatigue. The patient was offered a test for coronavirus but refused. A diagnosis of COVID-19 was given based on patient symptoms and PCR testing. The diagnosis of COVID-19 was initially and primarily made based on symptoms. The Centers for Disease Control and Prevention relaxed the criteria for diagnosing COVID-19. COVID-19 may be diagnosed without laboratory confirmation if the physician suspects the illness based on symptomology. The CDC states the most common symptoms of COVID-19 are: fever, cough, fatigue, anorexia, shortness of breath, sputum production, and myalgias, of which this patient had most. AD was treated with p.o. dosing of vitamin A (10,000 U/day), vitamin D (50,000 IU/day), Vitamin C (10,000mg/day) and iodine (50mg/day). All oral therapies were to be taken for four days, then

stopped. She was also treated with a dilute (0.04%) hydrogen peroxide (3cc in 250 cc of sterile, normal saline) solution along with 1 drop of 5% Lugol's iodine given via a nebulizer. She was instructed to nebulize 3 cc of the mixture every hour while awake and to gradually reduce the frequency as she mproved. Finally, she was treated with ozone given as an intramuscular injection with20 cc of 18 gamma ozone being injected into each buttock. On day 3 of her illness and one day after the start of treatment the patient reported marked improved in all symptoms. After the ozone injection at the office, she stated that her fever began lowering in 60 minutes and three hours later was resolved. The body aches, shaking and fatigue began to improve when the fever resolved. On day 4, 2-days after first treatment, the patient stated that her sense of smell and taste was improving. On day 5, the patient reported that all symptoms were gone except for minor fatigue which resolved a few days later.

Case 2:

CP is a 58-year-old white male who became ill 14 days before contacting our clinic. His initial symptoms were severe fatigue, sore throat and body aches. After a few days, they progressed to fevers fluctuating between 99.5- and 102-degrees Fahrenheit. He tested positive for SARS-CoV-2 antibodies seven days into his illness. He was instructed to self-quarantine at home and go the emergency room when his symptoms became unbearable. Over the next week, his symptoms worsened and new symptoms developed included loss of taste and smell and shortness of breath. The fatigue worsened to the point where he could not get out of bed to reach a glass of water. On day 17 of his illness we had a phone consult with the patient. CP was instructed to orally take: vitamin A (10,000 IU\day); vitamin D (50,000 IU/day); vitamin C (1,000 mg of ascorbic acid each hour until bowel tolerance and then take 75% of that amount daily, over 3 doses, morning, noon, and evening until further notice; and iodine (50 mg/day of Lugol's solution 5%). He was also advised to nebulize with a dilute hydrogen peroxide solution (0.04%) along with 1 drop of Lugol's 5% solution every waking hour until symptoms improved. After the second nebulized treatment CP reported he could start to feel the improvement in his breathing. —I could finally take a deep breath of air for the first time in many days. I no longer felt like I was going to die, he stated. At day 3 of treatment, he fever was still present but much lower, not going over 100.5 degrees Fahrenheit. The next day he was treated, in office, with an intramuscular injection of 20cc of 18 gamma ozone. After the ozone shot, he reported a dramatic improvement. The fever resolved within two hours and did not return. Later that day, his muscle aches and pains resolved. He made a full recovery over the next few days.

According to SIOOT, "After practicing Oxygen Ozone Therapy, the doctors found the following evidence: a general improvement in clinical conditions, normalization of body temperature, a reduction in C Reactive Protein (CRP), normalization of heart rate, an improvement in saturation and reduction in oxygen support, normalization of renal function (creatinine)."

Discussions :

Extracorporeal Hemotherapy with Ozone (EHO): Clinical Methodology In 1974, H.H. Wolff (1974) described a method in which a small quantity of blood was exposed to ozone in sealed glass bottles and then re-infused into the patient, stimulating interesting therapeutic responses (Wolff, 1974). So far, ozone has been used in therapy in an empirical way with encouraging anecdotal results reported (Bocci, 2006).

In the technique of ozone autohemotherapy (AHT), an aliquot of blood (50 to 500 ml) is withdrawn from a virally afflicted patient, anticoagulated, interfaced with a calibrated ozone/oxygen mixture,

then reinfused. This process is repeated serially, in a manner consonant with treatment protocols until viral load reduction and symptom abatement are observed. Another, more experimental and more intensive technique of oxygen/ozone gas administration, is called extracorporeal hemotherapy with ozone (EHO), which treats the entire blood volume using an ozone-resistant hollow-fiber oxygenator-ozonizer, much in the model of dialysis intervention (Bocci, 2013; Di Paolo, Gaggiotti & Galli, 2005). V. Bocci (2013) describes the caveats in using this method, not the least of which involves problems interfacing complex biomechanical machinery with a lethal agent. Given human ingenuity, however, these problems are solvable. This and similar methods are likely to be the most efficient in culling the massive virion waves that viremic episodes spawn. For the present time, however, AHT offers simpler—yet totally un-researched in Covid-19—interventions that involve only one venipuncture per treatment (while EHO requires two). Research is first needed to gauge EHO‘s viral culling action in innocuous Covid-19 surrogates.

Ozone, like any —medication offers both a therapeutic and toxic effect. When used based on established guidance, toxic effects are avoided (Shoemaker, 2010; Viebahn-Hänsler, 2003). Ozone is reported to activate the immune system in infectious diseases, (Bocci, 2007; Washutti, Viebahn & Steiner, 1990; Razumovskii & Zaikov, 1984) to improve the utilization of oxygen and stimulate release of growth factors and other mediators that may re-activate the immune system and reduce ischemia in vascular disease, now known to be a significant contributor to adverse Covid-19 outcomes (Washutti, Viebahn & Steiner, 1990; Bocci, 1996; Bocci et al., 1994).

Ozone is often strong anti-pathogenic and importantly is pathogen-agnostic, displaying similar oxidative biological properties to innate immune cells, thus has theoretical and practical attributes to make it a viable candidate as a COVID-19, MERS, and SARS viral load-reducing agent. Most research efforts on ozone's viricidal effects have centered upon its efficacy at breaking apart lipid molecules at sites of multiple bonds. When the lipid envelope of the virus is fragmented, its DNA or RNA core cannot survive. Ozone can also destroy capsid proteins of non-enveloped viruses.

However, the enveloped viruses are usually more sensitive to oxidative action compared to naked virions. The novel coronavirus is an enveloped virus thus likely has great susceptibility to clinical ozone therapy due to the fragility of their lipid-rich envelopes.

The extracorporeal technique named EHO offers substantial enhancements compared to traditional delivery methods. The technique of EHO in human patients is simple for hospital staff familiar with extracorporeal circulation. EHO was perfectly tolerated and showed promising therapeutic effects in various atheromatous and immune disease states. Pro-oxidant effects of blood ozonation can be monitored during clinical practice by simple blood tests such as the assay of plasma TBAR and PTG assays (Romero Valdés et al., 1993; Verrazzo et al., 1995; Molinari et al., 2014; Lintas et al., 2013; Berikhanova, Minenko & Bondarev, 2020).

Conclusion :

In conclusion, as our world becomes increasingly challenged by viral adversaries, the need for rapidly developing specific vaccines adapted to each viral species becomes evident. Yet, in parallel, research also needs to center on finding new methods of relieving the biological stress caused by onslaughts of viremic invasions that are common to many families of pathogenic viruses. The coronaviruses are a case in point, as they all possess lipid envelopes susceptible to structural modifications by ozone.

Thus, a proposal is herewith made that oxygen/ozone systemic therapies are granted research consideration for Covid-19 treatment of patients after acute circulatory disorders. Besides subjective outcome measurement, we propose to include a blood biomarker panel that is currently being used by Mass General and other Harvard hospitals to risk stratify infected populations. This will add novel objectivity to any conclusions about treatment efficacy. Such therapeutic approaches may then be found useful and more adoptable when accompanied by physiological evidence-based measures, not only in these specific coronavirus conditions, but also in a number of human lipid-enveloped viral pathogenic infections, and importantly for the future coronavirus epidemics that are certain to emerge.

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