JOURNAL OF CRITICAL REVIEWS

ISSN- 2394-5125 VOL 7, ISSUE 13, 2020

USE OF OZONE AS AN ADJUVANT THERAPY FOR PATIENTS WITH COVID-19 IN IRAQ. A COMPARISON STUDY WITH STUDIES FROM OTHER COUNTRIES.

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Received: 14 March 2020 Revised and Accepted: 8 July 2020

ABSTRACT: Recently, there has been a global demand toward finding vaccination or treatment for SARS-COV 2. The aim of this review is to study the effect of ozone therapy as a complementary therapy for patient with COVID-19 in different stages of disease, as well as reviewing the available supporting evidence from studies around the world.

Our study has been done between 15th of May and 1st of July, 2020 in Al Hussein Teaching Hospital, Al Muthanna Province, Iraq. Ninty Eight patients were included and their ages are between 21-78 years old in different stages of covid-19 disease. Systemic ozone therapy can be potentially useful in SARS-CoV-2. The rationale and mechanism of action has already been proven clinically in other viral infections and has been shown to be highly effective in research studies. Systemic ozone therapy can be potentially useful in SARS-CoV-2. In this study, a total of 98 patients included. We used ozonated saline which has been infused to 82 patients in "moderate" and "severe" stages of disease for 5-7 days and then followed up for the next 4 wks. In addition, 16 patients in "critical" stage has also started to receive ozonated normal saline. Ozone can be a useful, cheap and easy applicable to patients with SARS-CoV-2 with especially promising results if being started before "critical" stages of disease. And as early been given in stages of disease, as better results achieved and shorter hospitalization and faster recovery gained.

I. INTRODUCTION:

Coronaviruses are a large family of viruses which may cause illness in animals or humans. In humans, several coronaviruses are known to cause respiratory infections ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). The most recently discovered coronavirus causes coronavirus disease COVID-19 (WHO official website). WHO also mentioned that COVID-19 is the infectious disease caused by the most recently discovered coronavirus. This new virus and disease were unknown before the outbreak began in Wuhan, China, in December 2019. COVID-19 is now a pandemic affecting almost all countries globally. In February 2020, the World Health Organization designated the disease COVID-19 which stands for coronavirus disease 2019[1]. SARS-Co V2 is spread by human-to-human transmission via respiratory droplets or direct contact, and infection has been estimated to have a mean incubation period of 6.4 days and a basic reproduction number of (2.24-3.58) days[2].

Ozone is an oxidant that shows a paradoxical activity when in contact with organic molecules, thus causing a powerful antioxidant response[3]. In fact, ozone reacts with target substrates in biological fluids leads to the creation of hydroperoxides and aldehydes. It causes significant adaptive stress response, by stimulating anti-oxidizing and detoxifying enzymes expression. Hence a re-equilibration of the cellular redox state, which is fundamental process for inhibiting viral replication that will be blocked. By reacting with aldehydes, ozone generates hydroperoxides and particularly H_2O_2, it rapidly spreads through cells of the immune system. Ozone can inactivate viruses via direct oxidation of its components [4].

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Ozone therapy represents a useful complementary therapy but neither ozone, nor H_2O_2 reach sufficient concentrations in tissues because free pathogens are protected by plasma antioxidants and intracellular viruses are inaccessible[5]. It also bioregulates signals transduction thus promoting immune responses, modulating interferon and interleukins through the activation of NF-KB, thus increasing the release of cytokines. The paradoxical mechanism by which ozone (a potent oxidant) can induce an antioxidant response, is currently demonstrated not only at a proteomic level, but also at a genomic one. Oxidative stress and innate immunity have a key role in lung injury pathways that control the severity of acute lung injury during viral infections like SARS [6,7,8,9,10,11].

In 2002, the fact that human body is able to produce ozone to protect itself from infectious agent has been underlined. This happens by involving neutrophils and antibodies of the immune system which by producing ozone, use its oxidizing power in order to destroy bacteria and viruses present on cell wall [12]. VAC strains (Elstree strain) and H1N1 (influenza A), have shown a reduction up to 5 log 10 respectively in 40 and 30 minutes. These results show important changes in different virus strains morphology[13].

Another important characteristic of ozone therapy against COVID-19 infection is shown by the contrast ability toward severe hypoxemia, typical of this virus. Tests carried out using NIRS spectroscopy, led to increased oxygenation (in the given case, cerebral) shown by an increase of oxygenated hemoglobin and constant values of the non-oxygenated one[14]. Bocci and Paulesu explain the possibility that ozone may act *in vivo*[15]. The following mechanisms may have some relevance:

1- A prolonged ozone therapeutic treatment appears able to induce an adaptation to oxidative stress, hence a re-equilibration of the cellular redox state, which is a fundamental process for inhibiting viral replication that will be blocked.

2- The induction of cytokine synthesis, such as IFN and IL, in ozonated blood has been shown to be possible. Moreover, the release of heat shock proteins such as HSP60-90 are also influential in viricidal activity. These proteins are potent activators of the immune system, able to induce the synthesis of pro-inflammatory cytokines by the monocyte-macrophage system and the activation of antigen-presenting cells[16,17].

3- Oxygen-ozone therapy improve oxygenation[18,19]. The patient with SARS are prone to have non-specific hepatitis, lung fibrosis and renal failure may be present[20,21,22]. Ozone therapy stabilizes hepatic metabolism and fibrinogen and prothrombin plasma levels tend to normalize in infected patients, suggesting an improvement of the hepatic protein synthesis[23]. There is a lot of research demonstrating the protective effect of ozone to prevent oxidative damage to heart, liver, lung and renal tissue[24,25,26,27,28,29].

4- During blood ozonation in *vivo* for Major Autohemotherapy (MAH), using ozone concentrations near 90 µg/ml of blood, it may be feasible to induce the oxidation of free viral components, which could represent an inactivated and immunogenic vaccine[23,30,31].

Ozonated saline solution: this method is supported by a large amount of scientific papers and a strong clinical experience about the benefits of this therapy[32].

Unlike major autohemotherapy, the ozonized saline solution has proven to be especially effective in viral diseases such as Epstein Barr, Cytomegalovirus, Papillomavirus, Herpes Zoster, Herpes Simplex, etc. Since saline solution is a plasma expander, ozonated saline represents a greater amount of blood being treated than MAH and therefore, the number of sessions may need to be reduced.

An analysis of bibliographic data on the interaction of ozone with Sodium Chloride (NaCl) in aqueous solutions, allows us to conclude that the decomposition of ozone in aqueous solution of NaCl is not accompanied by formation of products other than oxygen[33,34]. When ozone dissolves in water, free radicals, hydrogen peroxide (in an insignificant amount), hexagonal water structures and small molecules are formed. Hexagonal water improves transport across cell membrane not only of electrolytes, but possibly also of other substances[35].

Therefore, ozone is a molecule which acts on different levels and in different physiological fields. We believe that it would be useful to utilize ozone as a complementary therapy used in addition to the current therapeutic protocols suggested by WHO in the treatment against COVID-19.

II. MATERIALS AND METHODS:

Covid-19 patients (with or without other comorbidities) who are tested positive by PCR are grouped in 4 stages according to their signs and symptoms, CT lung infiltration and other findings as follows:

A- Stage I (mild)
1- CT finding: -ve
2- Stable general condition
3- SpO_2 >90% on room air
4- Respiratory rate < 30 breath per minute (bpm)

ISSN- 2394-5125 VOL 7, ISSUE 13, 2020

B- Stage II (moderate)
1- CT findings: +ve and <40% of lung in infiltrated
2- Stable general condition
3- SpO_2 >90% on room air
4- Respiratory rate < 30 bpm
C- Stage III (severe):
1- CT findings: +ve with >50% of lung is infiltrated
2- SpO_2 <90 on room air and need oxygen through face mask.
3- SpO_2 > 90% on high FiO2
4- Respiratory rate > 30 bpm
5- No signs of ARDS, no other organ dysfunction as a squeal of Covid-19
D- Stage IV (critical):
1- ARDS (adult respiratory distress syndrome)
2- Respiratory rate > 35
3- SpO_2 < 90 % even when high FiO2 is delivered through face mask.
4- Need assisted ventilation (invasive or non-invasive)
5- +/- other organs dysfunction.

Mild cases (stage I) were excluded, while patients with stages II,III and IV were included in this study. Once patients were diagnosed, admitted to Covid-19 ward, and classified, an ozonated normal saline was started as a complementary therapy side by side with their medicinal regimen officially applied by Al-Muthanna Health Directorate and Iraqi Ministry of Health. A total 5-10 days period of ozonated saline therapy was conducted with 1-2 doses per day.

Recording the patient's response and their signs and symptoms, together with other criteria, were recorded and followed up. Those patients who show slow response, the therapeutic period was extended to 7-10 days or the total dose was set to 2 doses/day until their conditions are settled and they show marked improvement.

After completing sessions, a glutathione 1.2 g with 2 g vitamin C was given orally for once. Then after, a close monitoring for the patient was done to record any signs and symptoms of relapse.

III. RESULTS AND DISCUSSION:

China has explored important clinical trials on a host of possible effective treatment options including ozone therapy: " We introduced our experience in treating two confirmed cases by ozone therapy—major autohemotherapy (MAH)[36] . A case study of 2 patients were done and MAH was carried out to each patient for 7 days. After treatment, the two patients remitted symptoms and discharged with negative reverse transcription polymerase chain reaction testing for severe acute respiratory syndrome coronavirus". They found that ozone therapy may be responsible for the good effects observed in the two cases[37].

In a clinical study published at May 2020 and carried on in Italy, a group of researchers found that systemic ozone therapy can be potentially useful in SARS-CoV-2. The rationale and mechanism of action have already been proven clinically with other viral infections and have been shown to be highly effective in research studies. The mechanisms of action involved are the modulation of the NF-κB/Nrf2 pathway and IL-6/IL-1β expression. The modulation of these pathways by ozone therapy have an impact in the cytoptotection and blockage of viral replication[38].

In our study, the results goes with the previous studies and if ozone infusion starts early in disease, the results were more promising. All the patients with stage II & III of disease who received 5 days of ozonated saline (1-2 dose/day) have recovered and discharged from hospital.

A multicerntre clinical study done in Italy at June 2020 has evaluated the beneficial effects of the systemic Oxygen-Ozone (O_2O_3) in patients suffering from SARS COV-2 disease in the early phase of the disease, before worsening, up to the need of tracheal intubation.

The study is based on the rationale on the systemic (O_2O_3) treatment could be effective, positively influencing the disease evolution and /or being able to mitigate the onset of the cytokine storms syndrome at least partially[39].

The effect of ozonated saline in our study was complete recovery of patients with COVID-19 if ozone given early in disease. While no such results were gained if given in "critical" stage as most of the patients (62%

ISSN- 2394-5125 VOL 7, ISSUE 13, 2020

) died before successfully finishing 5 days of ozone. Notifying that all patients who finished 5 days of ozonated saline have recovered and tested –ve after 2 weeks.

In a study done by multi-nation researchers, hemotherapy versus usual care was determined. The primary outcome was time from hospital admission to clinical improvement, which was defined as either hospital discharge. Secondary outcomes were clinical improvement measured on the 7th, 14th and 28th day after admission, as well as time to a 2-fold reduction in concentrations of C-protein reactive, ferritin, D-dimer and lactate dehydrogenase. Nine patients (50%) received ozonated autohemotherapy beginning on the day of admission. In unadjusted comparisons, ozonated autohemotherapy was associated with significantly shorter time to clinical improvement and significantly higher proportion of patients achieving clinical improvement. They also found in their prospective cohort study on patients with severe pneumonia that " twice-daily ozonated autohemotherapy was associated with a clinically and statistically significant reduction in the time to clinical improvement. Risk-adjusted analyses confirmed the results of the unadjusted analyses. This cohort study provides novel new data pointing to the potential role of ozonated autohemotherapy for treatment of severe COVID-19 pneumonia"[40]

A group of researchers has published that "ozone is a molecule which acts on different levels and in different physiopathological fields. Therefore, we believe that it would be useful to propose this method as a support to the drug therapy currently in treatment against viral infections in general and particularly against COVID-19 and within an integrative medicine approach"[41]

And in a study published in Spain: "another potential effective therapy is ozone: it has been extensively studied and used for many years and its effectiveness has been demonstrated so far in multiple studies "[42]

And in a study published in May 2020, the researchers have recommended use of Ozone in all stages of disease and published: " Ozone has four proven biological properties that could allow its use as an alternative therapy in the different phases of SARS-CoV-2 infection. Ozone could inactivate the virus by direct (O3) or indirect oxidation and could stimulate the cellular and humoral immune systems, being useful in the early COVID-19 infection phase . Ozone improves gas exchange, reduces inflammation, and modulates the antioxidant system, so it would be useful in the hyper inflammation or cytokine storm phase, and in the hypoxemia and/or multi-organ failure phase"[43]

In our study, good results are associated with early administration of ozone in any stage before critical stage when multiorgan dysfunction begins and thromboembolism commence. This might be explained by once thromboembolism begins, no strong role for ozone to prevent thromboembolism. Hence, higher mortality rates occur in "critical" stage of disease.

And in a conclusion discussed several studies about ozone " it was concluded that ozone therapy is effective in controlling COVID-19 due to its antiviral, oxygenating, anti-inflammatory, oxidation balancing and immunomodulation effects"[44]

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