Utilization of Ozone as a Complementary Therapy for COVID-19 Patients

Article *in* International Journal of Psychosocial Rehabilitation · September 2020

DOI: 10.37200/IJPR/V24I7/PR271061

1 author:

Hekmat B Alhmadi
College of medicine, Al muthanna university, Iraq
12 PUBLICATIONS **4** CITATIONS

SEE PROFILE

International Journal of Psychosocial Rehabilitation, Vol. 24, Issue 07, 2020
ISSN: 1475-7192

Utilization of Ozone as a Complementary Therapy for COVID-19 Patients

Husham A. Razzaq, Mohammad S. Hasan, Muthanna F. Al-Dhalemy,
Wurood M. Al-Silaykhee, Hekmat B. Alhmadi, Zaid A. Majeed

Abstract--- *This study which has been done between 15th of May and 1st 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. Iraq reported its first confirmed cases of SARS-CoV-2 infections on 22 February in Najaf city.4 And by 7th of April, 28,414 tests have been done in Iraq as a whole, with 1202 of them turning positive. To our knowledge, no antiviral drugs to treat patients with COVID-19 nor any vaccine have been licensed in any country in the world so far.*

The scope of this study is to identify "the ozone utilization that serves as a complementary therapy" in management of COVID-19 patients.

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. In this study, 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 2 wks. In addition, 16 patients in "critical" stage has also been 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, shorter hospitalization and faster recovery gained.

Keywords--- *Ozone, COVID-19, SARS-COV-2.*

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

Husham A. Razzaq, M.B.Ch.B, F.I.B.M.S. (Anesthesia & ICU), F.I.P.P. Senior Anesthesiologist and Interventional Pain Specialist. Al Hussein Teaching hospital, Al Muthanna, Iraq.
Mohammad S. Hasan, M.B.Ch.B, D.T.M. Senior Respiratory Physician. Al Hussein Teaching Hospital, Al Muthanna, Iraq.
Muthanna F. Al-Dhalemy, M.B.Ch.B, D.T.M. Senior Respiratory Physician. Al Hussein Teaching Hospital, Al Muthanna, Iraq.
Wurood M. Al-Silaykhee, Department of Obstetrics. College of Medicine, AL-Muthanna University, Iraq.
Hekmat B. Alhmadi, Department of Chemistry. College of Medicine, AL-Muthanna University, Iraq.E-mail: Hb-Alhmadi@wiu.edu
Zaid A. Majeed, M.B.Ch.B, F.I.B.M.S. Department of surgery, College of Medicine, AL-Muthanna University, Iraq.

Received: 5 July 2020 | Revised: 12 July 2020| Accepted: 20 July 2020

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].

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 H_1N_1 (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 esplain 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

Received: 5 July 2020 | Revised: 12 July 2020| Accepted: 20 July 2020

improvement of the hepatic protein synthesis[16]. 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].
5. 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 MAH 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 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 < 25 breath per minute (bpm)

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 fields are infiltrated

Received: 5 July 2020 | Revised: 12 July 2020| Accepted: 20 July 2020

2. SpO_2 <90 on room air and need oxygen through face mask.
3. SpO_2 > 90% on supportive oxygen with low or high FiO_2
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. Ozone used was medical O2/O3 mixture with high purity O2 inlet to the ozone generator. The concentration of ozone used was 35-45 µg which was allowed to flow, bubbling freely in normal saline for 3-5 minutes. Then the ozonated saline was given to patients through wide bore cannula in 2 ways:

1. Infusing the ozonated saline mentioned above to the patient in a period not exceeding 15 minutes. If for a reason or another the period of giving this saline exceeded 15 min., then the ozone is added to the saline using 50 ml syringe and mixed with saline or the fluid is simply re-ozonated.
2. Infusing the ozonated saline directly while ozone is bubbling to deliver as much ozone as possible. . Ozonation period continues for 5-10 minutes in a semi-opened and well ventilated room to decrease the amount and concentration of ozone inhaled. This method has been given exclusively to medical staff as there is a lack of supplies and staff to use this method in all the patients.

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 show significant 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

A total of 98 patients were included in this study. Number of patients from each stage is illustrated in this figure.

Received: 5 July 2020 | Revised: 12 July 2020| Accepted: 20 July 2020

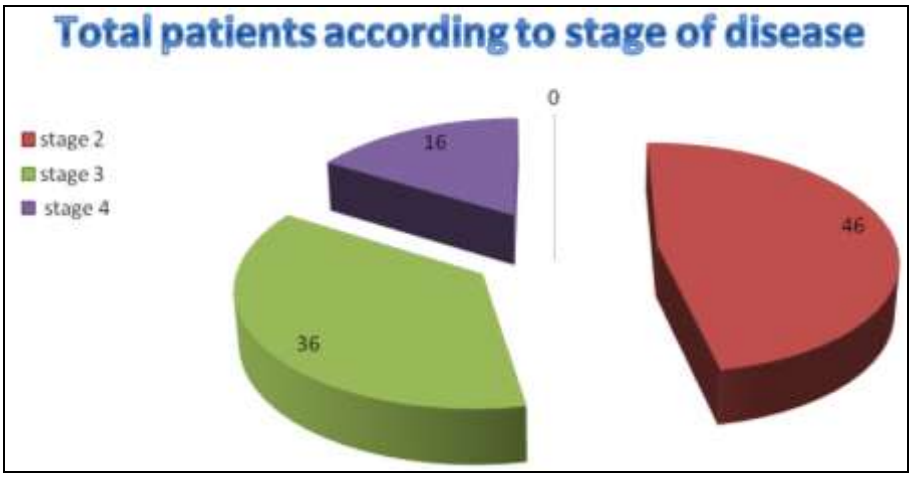

Fig 1: Number of all Patients Grouped According to Stage of Disease

All stage II patients (46 patients) who received 4-7 days of ozonated saline (fig.,2) were recovered and discharged from hospital later regardless of their sex (fig., 3) or comorbidities (fig.,4).

Indeed, most of patients described significant signs of improvement after 3 days of receiving ozonated saline.

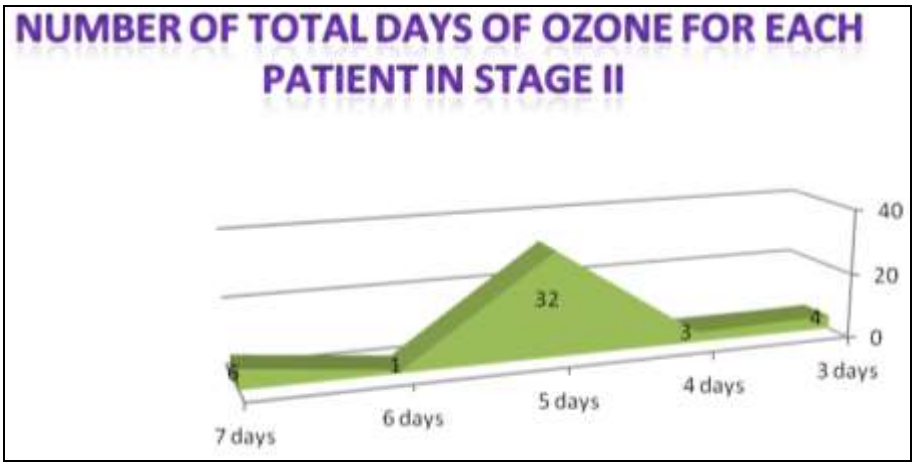

Fig 2: Shows Number of Patients and the Total Days of Receiving Ozone

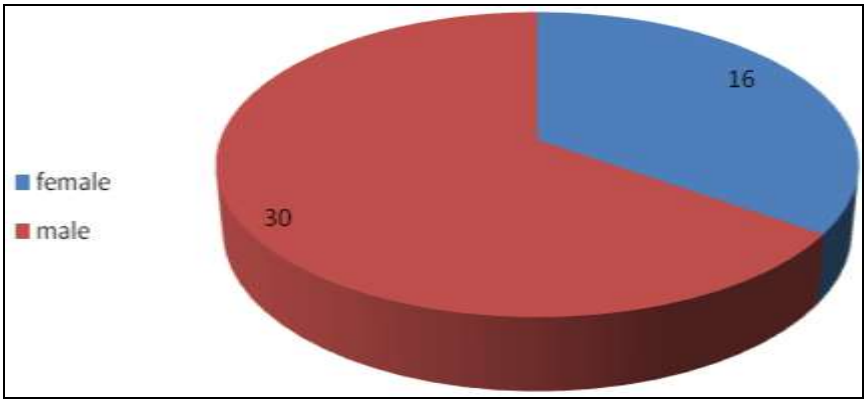

Fig 3: Shows Sex Variation in Stage II Patients

Received: 5 July 2020 | Revised: 12 July 2020| Accepted: 20 July 2020

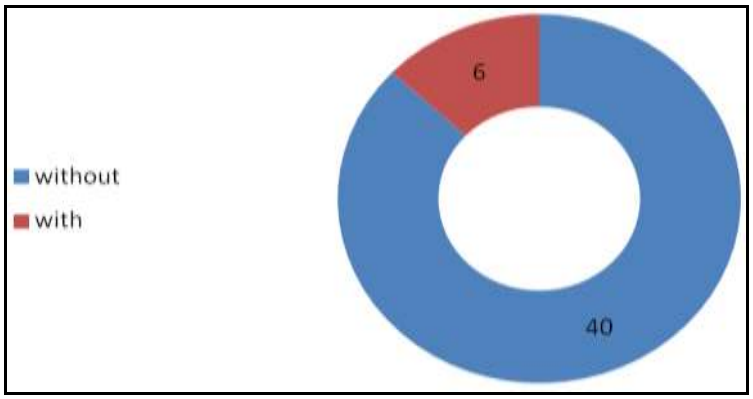

Fig. 4: Shows Presence of Comorbidities in Patients with Stage II of Disease

Age groups of patients with stage II is illustrated in figure 5 which demonstrates that main age groups affected are below 70 years old. This fact goes clearly with the fact that older age groups are mainly severely affected.

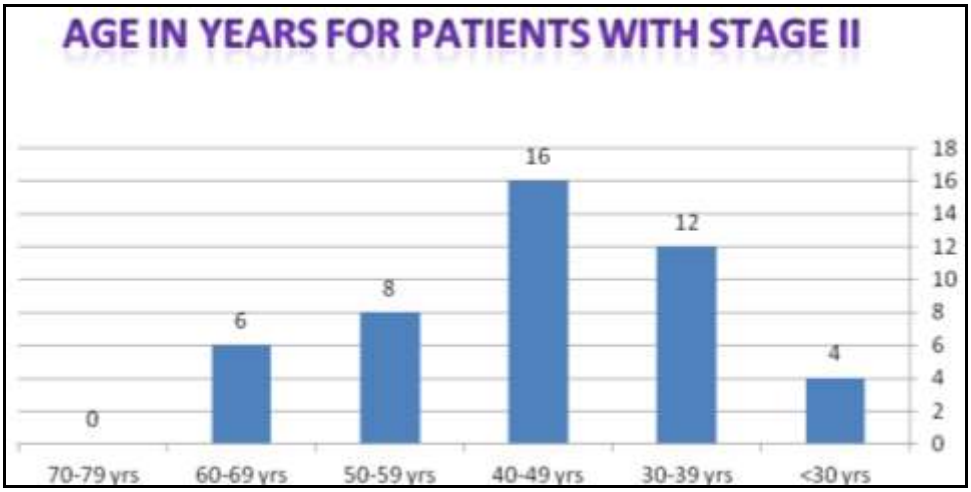

Fig. 5: Shows Age Distribution in Stage II Patients

These good and promising results might be due to enhanced effects of ozone as the major load of viruses still in blood and cells are still not invaded enormously by virus. In addition, the ozone may have enough time to exhibit its effects on immune element and enhance immune system to show antiviral activity.

Early administration of ozone in early stages of disease is accompanied by good outcome.

Patients with stage III has sex variation demonstrated in fig. 6.

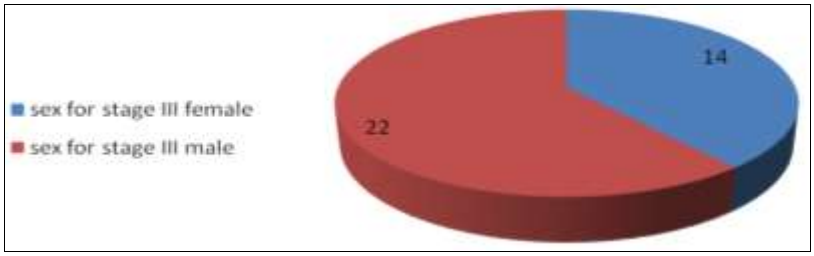

Fig. 6: Shows Number of Male and Female Patients with Stage III of Disease

Received: 5 July 2020 | Revised: 12 July 2020| Accepted: 20 July 2020

The distribution of age group is illustrated in fig. 7.

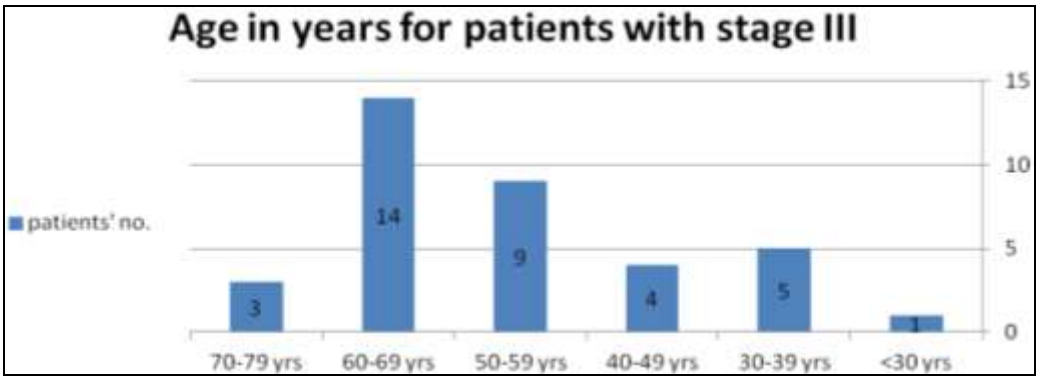

Fig. 7: Age Distribution for Patients with Stage III

Forty two patients in stage III admitted to Covid-19 unit have comorbidities as shown in fig. 8. Those comorbidities mainly include hypertension, type II diabetes mellitus and ischemic heart disease.

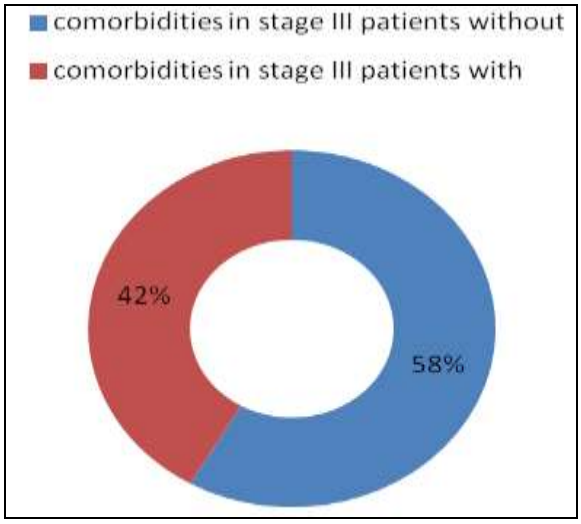

Fig. 8: Number of Patients with and without Comorbidities in Stage III of Disease

All the patients with stage III of disease who received 5-10 days of ozonated saline were recovered regardless of their ages or comorbidities (fig. 9).

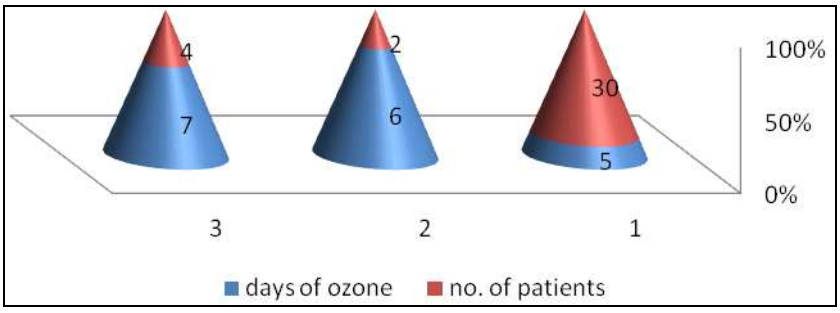

Fig. 9: Shows Number of Patients and the Total Days of Receiving Ozone. Stage III

Received: 5 July 2020 | Revised: 12 July 2020| Accepted: 20 July 2020

No one has been transformed to critical case or needed respiratory support, no fatalities were documented and indeed most of them started to assign improvement after receiving 3-5 days of ozone. This might be due to direct viricidal activity of ozone in relatively early stage of disease "while the patient still has viremia" and indirect promotary action of ozone which might needs few days to exhibit a noticeable action on immune system. As percent of viruses invade the cells and shift from intravascular to intracellular level, as fast as the multiorgan dysfunction develops, and as hard for the ozone to exhibit its supposed action and as poor outcome results.

For 16 patients with stage IV of disease, female to male ratio was 1:3 as (shown in fig. 10) and 44% were having comorbidities (mainly hypertension, type II diabetes mellitus and 1 patient had chronic obstructive pulmonary disease "COPD") Fig. 11

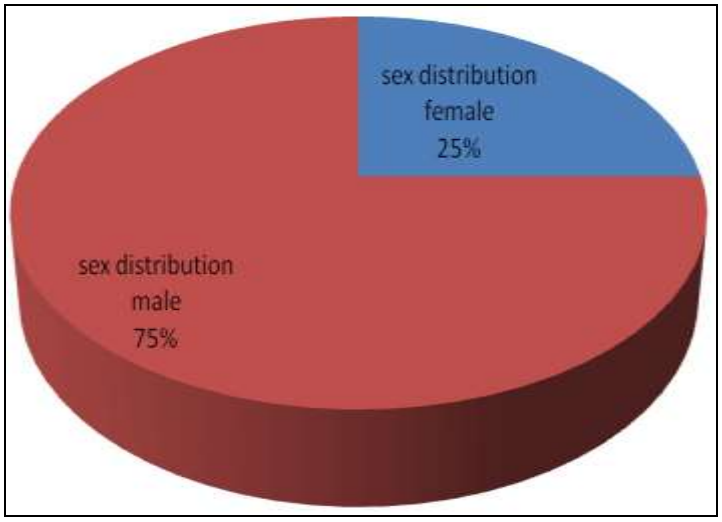

Fig. 10: Sex Distribution for Patients with Stage IV of Disease

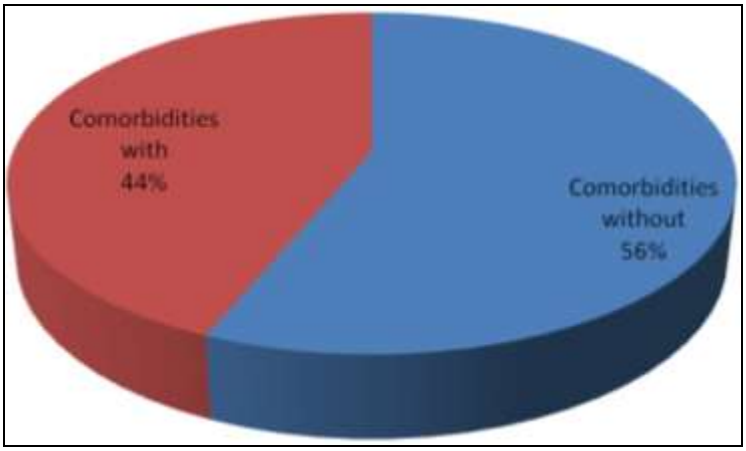

Fig. 11: Illustrates Presence of Comorbidities (with or without) in Patients with Stage IV of Disease

For patients with stage IV of disease, 6 patients out of 16 were recovered while, unfortunately, 10 patients died (fig.,12).

Received: 5 July 2020 | Revised: 12 July 2020| Accepted: 20 July 2020

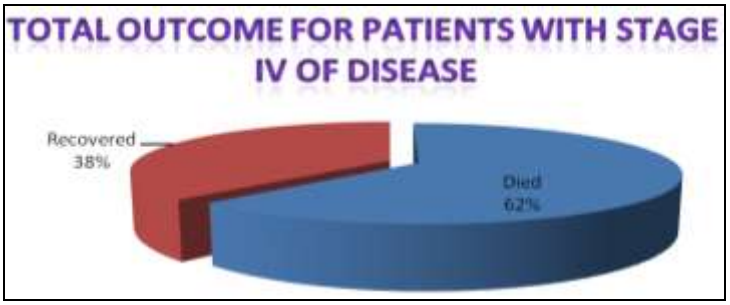

Fig. 12: Shows the Final Outcome for Stage IV Patients

All those who could receive 5 or more days of ozone therapy as shown in (fig. 13) and have been given one or more doses/day as shown in (fig. 14) have passed safely and declared full recovery from Covid-19. While all patients who are, unfortunately, declared dead, couldn't have enough time to continue their ozone doses for five or more days. They have died after 2 or 3 days from starting ozone therapy.

All the patients died in stage IV came to hospital at late stages, and did not have time to continue therapy and failed to receive complementary ozone for 5 days as shown in figure below.

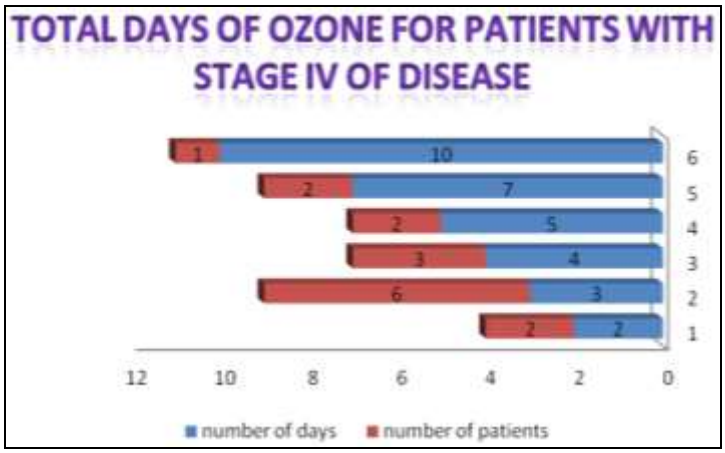

Fig. 13: Represents Total Days of Ozone Received by Stage IV Patients

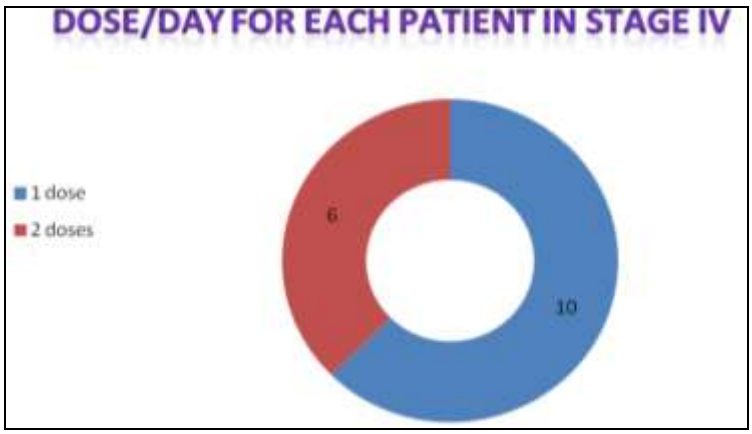

Fig. 14: Represents doses of Ozone per Day for Stage IV Patients

Received: 5 July 2020 | Revised: 12 July 2020| Accepted: 20 July 2020

Some of those patients developed signs of multiorgan dysfunction while others might show signs of thromboembolism such as rapid disturbance of level of consciousness, , tachypnea and sudden desaturation despite being on respiratory assisting machines (whether invasive or non-invasive). This might be (according to researchers opinion) due to insufficient time to promote the immune system. And the other possible reason might be the beginning of induction of widespread thromboembolism, in which ozone may not have a clinical effect or proved role to prevent this part of pathophysiology of Covid-19 syndrome.

All patients have taken ozonated saline for five days and more have survived and discharged from hospital except one patient who developed pneumothorax and collapsed Right lung probably due to assisted ventilation force or preexisting COPD.

A number of patients developed signs of multiorgan dysfunction which was a bad predictor for outcome. Red-color urine was described by 2 patients and they suffered from rapid deterioration after 24-48 hours, then died soon after.

IV. Conclusion

Ozone treatment represents a promising complementary therapy (together with medicinal protocols) and a hopeful work for patients with covid-19 patients, especially if has been given before stage IV of disease, before ARDS develops and multiorgan dysfunction occurs. Some patients required up to 10 days of ozonated saline while most of other patients showed signs of rapid improvement after 2 or 3 days of treatment.

Probably, no significant change in mortality noticed when ozone been administered in late stage of disease, when ARDS and multi-organ dysfunction developed, namely renal and hepatic malfunction have been recorded. In addition, it is a safe, side-effect free, cheap and affordable procedure in the absence of effective therapy or vaccine available so far.

As early stages of disease ozone's been started, as short hospital-stay gained and a good outcome achieved.

Patients with stage I of disease (just tested positive without CT findings) has been excluded because of lack of machinery and human resources.

V. Recommendations

A further and controlled studies with bigger samples and wider population to fortify the results of this study is recommended.

No one has shown any side effects through period of study or after as researchers noticed. That's encourage us to do more detailed studies with wider population. In addition, we recommend wide use of ozone therapy for Covid-19 patients worldwide as a complementary therapy together with recommended therapeutic protocols as Covid-19 syndrome continues to cause catastrophic outcomes and harvesting many lives all over the world in the absence of effective treatment and/or vaccines up to date.

Received: 5 July 2020 | Revised: 12 July 2020| Accepted: 20 July 2020

REFERENCES

[1] WHO. World Health Organization. Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020 (Accessed on March 3, 2020). 2020.

[2] Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. *Int J Antimicrob Agents.* Feb 17 2020:105924.

[3] Jiang HJ, Chen N, Shen ZQ, Yin J, Qiu ZG, Miao J, Uang ZQ, Shi DY, Wang HR, Wang XW, Li JW, Yang D, JIN M. Inactivation of poliovirus by ozone and the impact of ozone on the viral genome. *Biomed Environ Sci* 2010; 32:326-331.

[4] Murray BK, Ohmine S, Tomer DP, et al. Virion disruption by ozone-mediated reactive oxygen species. *J Virol Methods.* Oct 2008; 153(1):74-77.

[5] Burgassi S, Zanardi I, Travagli V, Montomoli E, Bocci V. How much ozone bactericidal activity is compromised by plasma components? *J Appl Microbiol.* May 2009; 106(5): 1715-1721.

[6] MARTINEZ-SANCHEZ G. Mechanisms of action of O3. Genomic pathways. *Ozone Therapy Global Journal.* 2019 2019;9(1):21-22.

[7] Delgado-roche L, Riera-romo M, Mesta F, Hernández-matos Y, Barrios JM, Martínez-sánchez G. Medical Ozone Promotes Nrf2 Phosphorylation Reducing Oxidative Stress And Proinflammatory Cytokines In Multiple Sclerosis Patients. *Rev Esp Ozonoterapia*. 2018 2018;8(2 Supp 1):48-49.

[8] Martinez-sanchez G, Delgado-roche L. Up-date on the mechanisms of action of ozone through the modification of cellular signaling pathways. Role of Nrf2 and NFkb. *Rev Esp Ozonoterapia*. 2017 2017; 7(2): 17-18.

[9] Bocci V, Valacchi G. Nrf2 activation as target to implement therapeutic treatments. *Front Chem.* 2015; 3:4.

[10] Martinez-sanchez G, Bordicchia M, et al. Is ozone pre-conditioning effect linked to Nrf2/EpRE activation pathway in vivo? *A preliminary result. Eur J Pharmacol.* Nov 5 2014; 742: 158-162.

[11] Pecorelli A, Bocci V, Acquaviva A, et al. NRF2 activation is involved in ozonated human serum upregulation of HO-1 in endothelial cells. *Toxicol Appl Pharmacol.* Feb 15 2013; 67(1): 30-40.

[12] Imai Y, Kuba K, Neely GG, et al. Identification of oxidative stress and Toll-like receptor 4 signaling as a key pathway of acute lung injury. *Cell.* Apr 18 2008; 133(2): 235-249.

[13] Murray BK, Ohmine S, Tomer DP, Jensen KJ, Johnson FB, Kirsi JJ, Robison RA, O'neill KL. Virion disruption by ozone-mediated reactive oxygen species. *J Virol Methods* 2008; 153: 74-77

[14] Molinari F, Simonette V, Franzini M, Pandolfi S, Vaiano F, Valdenassi L, Liboni W. Ozone autohemotherapy induces long-term cerebral metabolic changes in multiple sclerosis patients. *Int. J. immunopathol pharmacol* 2014; 27: 379-389.

[15] Bocci V, Paulesu L. Studies on the biological effects of ozone 1. Induction of interferon gamma on human leucocytes. *Haematologica.* Nov-Dec 1990; 75(6): 510-515.

[16] Bocci V. Ozone: A new medical drug. *Netherlands: Springer;* 2011.

[17] Larini A, Bocci V. Effects of ozone on isolated peripheral blood mononuclear cells. *Toxicol in Vitro.* Feb 2005; 19(1): 55-61.

[18] Lintas G, Liboni W, Simonetti V, et al. Long-term cerebrovascular reactivity mediated by ozone autohemotherapy: a NIRS study. Paper presented at: *Terzo Congresso del Gruppo Nazionale di Bioingegneria;* 2012, 2012.

[19] Zaky S, Fouad EA, Kotb Him. The effect of rectal ozone on the portal vein oxygenation and pharmacokinetics of propranolol in liver cirrhosis (a preliminary human study). *British Journal of Clinical Pharmacology.* Mar 2011 2011; 71(3): 411-415.

[20] Guan YJ, Tang XP, Yin CB, Yi ZQ. [Study on the damage of liver in patients with SARS]. *Zhongguo Wei Zhong Bing Ji Jiu Yi Xue.* May 2004; 16(5):267-270.

[21] Venkataraman T, Frieman MB. The role of epidermal growth factor receptor (EGFR) signaling in SARS coronavirus-induced pulmonary fibrosis. *Antiviral Res.* Jul 2017; 143: 142-150.

[22] Khan G. A novel coronavirus capable of lethal human infections: an emerging picture. *Virol J.* Feb 28 2013; 10:66.

[23] Simonetti V, Quagliariello V, Franzini M, Iaffaioli RV, Maurea N, Valdenassi L. Ozone Exerts Cytoprotective and Anti-Inflammatory Effects in Cardiomyocytes and Skin Fibroblasts after Incubation with Doxorubicin. *Evid Based Complement Alternat Med.* 2019; 2019: 2169103.

Received: 5 July 2020 | Revised: 12 July 2020| Accepted: 20 July 2020

[24] Delgado-ROCHE L, Hernandez-matos Y, Medina EA, Morejon DA, Gonzalez MR, Martinez-sanchez G. Ozone-Oxidative Preconditioning Prevents Doxorubicin-induced Cardiotoxicity in Sprague-Dawley Rats. *Sultan Qaboos Univ Med J.* Aug 2014; 14(3): e342-348.

[25] Adali Y, Eroglu HA, Makav M, Guvendi GF. Efficacy of Ozone and Selenium Therapy for Alcoholic Liver Injury: An Experimental Model. *In Vivo.* May-Jun 2019; 33(3): 763-769.

[26] Tezcan AH, Ozturk O, Ustebay S, Adali Y, Yagmurdur H. The beneficial effects of ozone therapy in acetaminophen-induced hepatotoxicity in mice. *Pharmacol Rep.* Apr 2018; 70(2): 340-345.

[27] Kaldirim U, Uysal B, Yuksel R, et al. Ozone therapy ameliorates paraquat-induced lung injury in rats. *Exp Biol Med (Maywood).* Dec 2014; 239(12): 1699-1704.

[28] Wang L, Chen H, Liu XH, et al. Ozone oxidative preconditioning inhibits renal fibrosis induced by ischemia and reperfusion injury in rats. *Exp Ther Med.* Dec 2014; 8(6): 1764-1768.

[29] Bocci V, Zanardi I, Travagli V. Ozonation of human HIV-infected plasmas for producing a global vaccine: How HIV-patients may help fight the HIV pandemia. *Virulence.* May-Jun 2010; 1(3): 215-217.

[30] Bocci V, Travagli V, Zanardi I. The failure of HIV vaccines: a new autovaccine may overcome some problems. *Medical Hypotheses.* Jun 2009 2009; 72(6): 662-664.

[31] Maslennikov OV, Kontorshikova CN, Gribkova IA. *Ozone therapy in Practice. Health Manual, Ministry Health Service of The Russian Federation The State Medical Academy Of Nizhny Novgorod, Russia. http://www.absoluteozone.com/assets/ozone_therapy_in_practice.pdf*. 1 ed2008.

[32] International Scientific Committee of Ozone Therapy. March13, 2020: 10

[33] Boyarinov GA, Gordetsov AS, Peretyagin SP, Matusyak KS, Ovchinnikov YV, Boyarinova LV. The analysis of interaction of ozone and sodium chloride in Aqueous solution. *Rev Esp de Ozonoterapia.* 2016; 6(Supp 1):77.

[34] Gorbunov SN, Korhouknov AE, Mozhaev MV, et al. [Structural-molecular transformations of water solutions of electrolytes under the influence of medical ozone]. *Meditsinskii almanakh.* 2013 2013(3):38-40.

Received: 5 July 2020 | Revised: 12 July 2020| Accepted: 20 July 2020