RESEARCH ARTICLE / *Araştırma Makalesi*

Outcomes of Ozone Therapy Administered as Prophylaxis or Treatment To Health Workers During The Covid-19 Pandemic

Sağlık Çalışanlarına Covid 19 Pandemisi Sırasında Proflaktik veya Tedavi Amaçlı Uygulanan Ozonterapinin Etkileri

Ülkü Aygen Türkmen, Derya Tan, Oğuz Özakın, Ahmet Yaser Müslümanoğlu, Döndü Genç Moralar, Ruhi Çakır, Serhat Soylu, Ayfer Kaya Gök

University of Health Sciences Istanbul Gaziosmanpasa Training and Research Hospital, Department of Anesthesiology and Reanimation, Istanbul

Yazışma Adresi / *Correspondence:*
Derya Tan

University of Health Sciences Istanbul Gaziosmanpasa Training and Research Hospital Department of Anesthesiology and Reanimation
E-mail: **drytn@hotmail.com**

Geleneksel ve Tamamlayıcı Anadolu Tıbbı Dergisi 2022,4(1):9-16

Ülkü Aygen Türkmen: https://Orcid.Org/ 0000-0002-7280-6420
Derya Tan https://Orcid.Org/ 0000-0001-9647-1541
Oğuz Özakın https://Orcid.Org/ 0000-0001-5138-1606
Ahmet Yaser Müslümanoğlu https://Orcid.Org/ 0000-0002-8691-0886
Döndü Genç Moralar https://Orcid.Org/ 0000-0002-4229-4903
Ruhi Çakır https://Orcid.Org/ 0000-0002-3232-9662
Ayfer Kaya Gök https://Orcid.Org/ 0000-0002-9021-8542
Serhat Soylu https://Orcid.Org/ 0000-0003-3886-5424

Abstract

Health employees are at high risk for COVID-19 infection. At the same time, the need for healthcare professionals has increased during the pandemic process. And it is clear that we have to protect our employees, ozone is a beneficial method which has not any side effects. Therefore, it is important to minimize the transmission risk of health employees and to support their immune systems. There are several studies demonstrating that ozone therapy supports the immune system. Moreover, ozone has proven to be highly effective in inactivating bacteria, fungi, molds and viruses both on the surfaces and suspended in the air. Ozone might be effective on coronavirus as well. In this study our findings will show protective effect of ozone on health employees. It is considered that ozone therapy is beneficial as a choice to increase protection methods and as supportive treatment for health employees. In our study, we aimed to examine the results of prophylactic or therapeutic ozone therapy which was applied to volunteer health employees during the COVID-19 pandemic.

Keywords Coronavirus, ozone therapy, health employees

Öz

Sağlık çalışanları COVID-19 enfeksiyonu için yüksek risk altındadır. Aynı zamanda pandemi sürecinde sağlık çalışanlarına olan ihtiyaç da artmıştır. Sağlık çalışanlarımızı korumamız gerekliliği kaçınılmazdır, ozon hiçbir yan etkisi olmayan faydalı bir yöntemdir. Bu nedenle sağlık çalışanlarına bulaş riskini en aza indirmek ve bağışıklık sistemlerini desteklemek önemlidir. Ozon tedavisinin bağışıklık sistemini desteklediğini gösteren birçok çalışma bulunmaktadır. Ayrıca ozonun hem yüzeylerde hem de havada asılı halde bulunan bakteri, mantar, küf ve virüsleri etkisiz hale getirmede oldukça etkili olduğu kanıtlanmıştır. Ozon, koronavirüs üzerinde de etkili olabilir. Bu çalışmada bulgularımız ozonun sağlık çalışanları üzerindeki koruyucu etkisini gösterecektir. Ozon tedavisinin, sağlık çalışanlarını koruma yöntemlerini artırmada ve destekleyici tedavi olarak faydalı olduğu düşünülmektedir. Çalışmamızda, COVID-19 pandemisi sürecinde gönüllü sağlık çalışanlarına uygulanan profilaktik veya terapötik ozon tedavisinin sonuçlarını incelemeyi amaçladık.

Anahtar kelimeler *Koronavirüs, ozonterapi, sağlık çalışanları*

INTRODUCTION

It is a definite necessity to support the immune system in order to minimize infection of health employees during the COVID-19 pandemic. At the same time, it is necessary for infected health employees to recuperate quickly and continue their work healthily. Due to the intense working conditions of health employees with excess workload and changes in family organization, the risk of infection due to the COVID-19 pandemic involves the fear of transmitting the infection to parents and children.[1]

The World Health Organization (WHO) reported that there have been 22,073 health employees with COVID-19 diagnosis in 52 countries since April 2020. The International Nursing Council announced this number as 90,000.[2] In Turkey, as of 26 July 2021, 436 health employees had died due to COVID19.[3] Though health employees may have recovered from disease, bodily and mental follow-up is important. With the presence of anti-spike or anti-nucleocapsid IgG antibodies, the risk of reinfection with SARS-CoV-2 is significantly reduced within the next six months. However, even if health employees with close contact during the pandemic have recovered from the disease, the risk may increase again six months later.[4]

It is considered that ozone therapy is beneficial as a choice to increase protection methods and as supportive treatment for health employees. Ozone gas (O3) is a molecule with three oxygen atoms found in the middle of the 19th century. The effect mechanism is inactivation of bacteria, viruses, fungi, yeasts and protozoa, stimulation of oxygen metabolism and activation of the immune system. The use of the molecules in gas form as medication is not very common and as a result, there is a need to develop special administration techniques for safe use of O3.[5]

Among the potential benefits of this therapy are reduced tissue hypoxia and hypercoagulation, preserved renal and cardiac organ functions, modulation of immune functions, improvement of phagocytic functions and inhibition of viral replication. Ozone may cause release and modulation of interferons (IFN) and may modulate cytokines like interleukin-2 (IL-2), IFN-γ and tumor necrosis factor (TNF) and colony-stimulating factors and stimulate phagocytic functions. These create very positive effects during COVID-19 infection.[6]

In recent years, a potential effect of ozone of in vivo viral inactivation was found.3 Studies also reported the efficacy and reliability for ozone therapy for Human Immunodeficiency Virüs(HIV), hepatitis C, Ebola and flu patients.[7-9]

Ozone therapy generally lasts 30 minutes and may be accepted as very safe with a complication rate of only 0.7 adverse effects per 100,000 treatments (0.0007%).[10]

The aim of the study is to analyze the clinical status and assess laboratory findings in terms of morbidity and mortality by investigating files of health employees with ozone therapy for treatment or prophylactic purposes. Participants included health employees attending our Traditional and Complementary Medicine center voluntarily with prophylactic or inpatient treatment who worked actively in a COVID-19 pandemic hospital, in COVID-19 clinics, isolation wards and intensive care or emergency services who used personal protective equipment.

MATERIAL and METHODS

The observation files and hospital information management system (HIMS) were retrospectively screened for male and female health employees of the COVID-19 pandemic hospital with 20-65 years of age who requested ozone therapy and were admitted, who attended the Traditional and Complementary Medicine Center after 20 March 2020 and provided informed acceptance and consent. Total 561 health employees were included in the study, 48 of them were intensive care nurses, 513 of them were from wards. Information such as demographic data, purpose of administration (prophylaxis or treatment), administration route, dose and frequency for ozone therapy, presence of

symptoms, comorbid diseases, length of hospital and intensive care stay, real time polymerase chain reaction (RT-PCR)data and thoracic computed tomography (CT) involvement were recorded.

Inclusion criteria for the study were defined as files of health employees with attendance at the Traditional and Complementary Medicine center, providing written acceptance and consent, age 2065 years, male or female, working in the COVID-19 pandemic hospital, receiving ozone therapy on their own request and with admission.

Exclusion criteria encompassed health employees with no association with COVID-19 and their files.

Sample Size

The sample size required for the study was calculated in terms of the PCR positivity rates before and after the treatment. Given the Type-I error rate $\alpha = 0.05$ for a two-sided test, and the power 80%, it is expected to age 15 to detect a 50% decrease in PCR positivity from pre-treatment to post-treatment.[11]

Statistical Analysis

Numerical data were summarized by mean±standard deviation along with median(minimum-maximum), whereas frequency and percentage as n (%) was used for categorical data. Comparisons between groups were evaluated by Chi-Square test or Fisher's Exact. T-test for two dependent ratios was used for the comparison of PCR positivity rates before and after treatment.[12] P <0.05 value was considered as statistically significant. Analyzes were performed using the R statistical programming language (version 3.6.3, R Core Team, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Of the 53 patients included in the study, 26 were female (49.1%) and 27 were male (50.9%). Mean age of patients was 35.7±10 years (minimum:22-maximum:66). The demographic information for patients is given (Table 1), with major autohemotherapy (MAH) doses, saline ozone (SO3) doses, clinical characteristics (comorbid diseases, frequency of clinical symptoms), unit of employment, length of hospital and intensive care stay given in Tables 2,3,4.

Table 1. Demographical data

F/M n (%)	26 (49.1) / 27 (50.9)
Age (year)	35.7±10
	33 (22-66)
Height (cm)	170.1±7.6
	170 (155-186)
Weight (kg)	73.6±10.4
	74 (49-99)
BMI (kg/m^2)	25.4±2.9
	25 (18.7-33.9)
Concomitant Disease	
Mitral valve disease n (%)	1 (1.9)
Autoimmune disease n (%)	1 (1.9)
Type-1 Diabetes n (%)	1 (1.9)
None n (%)	50 (94.3)

n (%) was given for categorical data, mean±standard deviation and median(minimum-maximum) were given for numerical data. F: female, M: male, BMI: body mass index.

Table 2. Ozone doses

	n (%)		n (%)
Ozone MAH dose mcg/ml		Saline Ozone dose mcg/ml	
None	17 (32.1)	None	27(50.9)
10-40	3(5.7)	0,1-0,4/3x100	1(1.9)
15-30	1(1.9)	0,1-1gama/3x100	1(1.9)
15-35	1(1.9)	1-3gama/3x100	1(1.9)
15-40	16 (30.2)	1-5gama/3x100	1(1.9)
20-25	1 (1.9)	1-5gama/3x100	1(1.9)
20-35	1 (1.9)	1-5gama/5x100	1(1.9)
20-40	8 (15.1)	3-5gama/3x100	1(1.9)
25-40	2 (3.8)	3gama/3x100	15(28.3)
30-40	3 (5.7)	5gama/3x100	5(9.4)

MAH: Major autohemotherapy

Table 3. Symptoms of patient	
Symptoms	
Fever	3(5.7)
Fever and cough	6(11.3)
Headache	5(9.4)
Sore throat	1(1.9)
Arthralgia	1(1.9)
Fatigue	2(3.8)
Loss of smell	1(1.9)
Cough	3(5.6)
None	31(58.5)
n (%) was given for categorical data, mean±standard deviation and median(minimummaximum) were given for numerical data. ICU: Intensive Care Unit.	

Table 4. Specifications of patients working place and hospitalization	
Unit	n (%)
Family Medicine	1(1.9)
Chief physician	2(3.8)
Traditional and Complementary Medicine Center	1(1.9)
Ward	21(39.6)
ICU	28(52.8)
Hospitalization	
Yes/No	10(18.9)/43(81.1)
Length of Hospital Stay (days)	8.7+4.2 6.5(5-17)
ICU Stay	
Yes/No	1(1.9)/52(98.1)
Length of ICU Stay (Days)	11
n (%) was given for categorical data, mean±standard deviation and median (minimum -maximum) were given for numerical data. ICU: Intensive Care Unit.	

Before treatment, 27 of all patients (50.9%) had positive PCR test while no patient had positive PCR result after treatment (p<0.001) (Table 5).

Table 5. PCR and CT Results	
Pre-treatment PCR	
Negative	26(49.1)
Positive	27(50.9)
Post-treatment PCR	
Negative	53(100)
Positive	0(0)
CT	
Negative	24(45.3)
Positive	22(41.5)
None	7(13.2)
PCR: Polymerase Chain Reaction; **CT:**Computed Tomography	

Ozone therapy was started to the patients at the day of diagnosis, and continued for 10 sessions. It has been planned once a day and lasted for 10 days. PCR test control is done 7th and 9th days.

Among the 23 patients with positive computed tomography (CT) results, 1 (4.5%) was PCR negative before treatment and 22 (95.5%) were positive (p<0.001) (Table 6). Of the 21 people working in wards, 13 (61.9%) had positive PCR before treatment, while 11 of the 28 people (39.3%) working in intensive care were positivity identified (p=0.154) (Table 6).

Of the 16 people working in the wards with CT taken, 6 (37.5%) had negative CT results, while 17 of the 26 people working in intensive care with CT taken (65.4%) had negative CT results (p=0.113).

For those working in wards, all 6 people with negative CT results had negative PCR results before treatment, while none of the 10 people with positive CT result had negative PCR result before treatment (p<0.001) (Table 6).

For those working in intensive care, 14 out of 17 people with negative CT result (93.3%) had negative PCR result before treatment, while 1 out of 9 people with positive CT result (6.7%) had negative PCR result before treatment (p=0.001) (Table 6).

Table 6. Relationship between CT and the unit and the pre-treatment PCR results

Pre-treatment PCR					
			Negative	**Positive**	**p[1]**
CT		Negative	21(87.5)	3(12.5)	**<0.001**
		Positive	1(4.5)	21(95.5)	
Unit		Ward	8(3.1)	13(61.9)	0.154
		ICU	17(60.7)	11(39.3)	
CT					
			Negative	**Positive**	**p[1]**
Unit		Ward	6(37.5)	10(62.5)	0.113
		ICU	17(65.4)	9(34.6)	
Pre-treatment PCR					
Unit	**CT**	**Negative**	**Positive**	**Total**	**p2**
Ward	Negative	6(100)	0(0)	6(37.5)	<0.001
	Positive	0(0)	10(100)	10(62.5)	
ICU	Negative	14(93.3)	3(27.3)	17(65.4)	0.001
	Positive	1(6.7)	8(72.7)	9(34.6)	

[1]Data were summarized as n(%). P values are based on Chi-Square test. ICU: Intensive Care Unit; 2Data were summarized as n(%). P values are based on Fisher's Exact test. ICU: Intensive Care Unit; PCR: Polymerase Chain Reaction; CT:Computed Tomography

DISCUSSION

During the COVID-19 pandemic in our hospital, in addition to the use of personal protective equipment (PPE), those receiving ozone therapy as protective precaution and/or asymptomatic/symptomatic COVID-19 positive health employees receiving ozone therapy were assessed with the aim of monitoring the efficacy of this treatment.

When demographic data are analyzed, the mean age of health employees was 35.7 years. The young age of nurses, doctors and other support personnel teams working in wards and intensive care and low comorbid diseases is one of the factors in the rapid recovery of health employees in spite of illness.

One of the reasons for the rapid rate of spread is the close contact between health employees. Additionally, intense working tempo, remaining in PPE for hours in a humid environment and fatigue are present which increase the probability of easy disease transmission.

The traditional and complementary medical center offers both major autohemotherapy (MAH) and saline ozone methods in our clinics and intensive care units with specialist doctor opinions. Patients have 10-40 mcg/mL MAH and 0.1-5 mcg/mL dose of medical ozone gas applied in a O2/O3 mix with Saline. Health employees without any clinical symptoms, without CT involvement and PCR (-) had ozone therapy administered for the purpose of strengthening their immune systems with prophylactic aims beginning with low dose and slowly increasing the dose. Employees with COVID-19 diagnosis generally had ozone therapy applied during admission or in our center. The most commonly encountered symptoms were identified as fever and cough.

In sepsis, the role of host immunity is important for survival. With developments in supportive treatments, deaths during the early stages of septic shock was significantly reduced. However, in the majority of survivors, a long-term immunosuppression phase occurs after the initial inflammatory phase. For this reason, the strategy called 'a new path' to fight virulent pathogens offers a new approach to

strengthen host immunity with the immunomodulation route and the use of immunomodulation agents is recommended.[13] Modulation of the immune reactions via molecules which modulate the relationship between immunity and pulmonary microbiom or directly affect the virus life cycle are proposed to be very important for new immunotherapeutic planning to reduce the current COVID-19 pandemic. With this aim, the main targets of a study about O2/O3 treatment were reported to be prevention of the cytokine storm (inflammation markers CRP ≤30%, IL6 ≤25%), reduction of D-dimer (≤35%), and improvement of respiratory functions and oxygen parameters (O2 saturation ≥10%, PaO2/FiO2 ≥6%).[14]

Ozone therapy stimulates many cytokines including (IL-2), one of the main cytokines. It permits increases and proliferation of lymphocytes in lymphoid tissue. It is reported to regulate proliferation, differentiation and maturation of stem cells responsible for the production of granulocyte-macrophage colony stimulating factor, macrophage colony stimulating factor and white blood cells.[15]

With many evidence-based studies and cheapest administration, ozone therapy is not an antibiotic on its own; however, it has anti-infective effect and improves a variety of physiological parameters required for infection defense.[16] All health employees with COVID-19 diagnosis had inflammation markers, respiratory parameters and oxygen indexes monitored and identified to improve. The aim of this study was to monitor the effects on clinical progression of those receiving ozone therapy as a complementary treatment for health employees who were PCR positive and had lung involvement. For this reason, this study did not report the laboratory findings of our employees with COVID-19 diagnosis. All our employees had negative PCR tests at the end of treatment.

Personal protective equipment is recommended for the purpose of protecting health employees. However, there is low evidence that better protection is caused by covering larger areas of the body. Generally, this means more difficulty in wearing and taking off PPE, less user comfort and higher levels of transmission. Health sector employees exposed to high-risk infectious diseases should record the use of PPE and it is reported necessary to prospectively monitor health sector employees in terms of infection risk.[17]

In our study, though not statistically significant, 61.9% of employees in wards were PCR positive before treatment while 39.3% of intensive care employees were positive. The higher PCR positivity rates among ward health employees may be due to inappropriate use of PPE. For this reason, ozone therapy plays an important role in increasing antioxidant capacities and fighting against infection.

The outcomes of two severe cases with COVID-19 showed ozone therapy supports the improvement of clinical status and chest CT images and shortens the duration of viral transmission and hospitalization.[18]

In our study, the majority of our health employees were comprised of doctors, nurses and personnel from wards (39.6%) and intensive care units (52.8%) monitoring and treating COVID-19 patients. The hospitalization rate was 18.9% and number of days of admission were 6.5. It is possible to say that health employees receiving ozone therapy had shorter hospitalization duration compared to COVID-19 patients not receiving ozone in the literature. Our health employees received some treatment in line with national guidelines. There was no intervention to treatment as this study retrospectively screened files. Only one of our health employee patients required intensive care. They were discharged from intensive care after 11 days with noninvasive mechanical ventilation and high flow nasal cannulation (HFNC) support treatment.

Systemic ozone therapy (OT) may have potential benefit for clinical management of a variety of complications linked to SARS-CoV-2. A review by Martinez-Sanchez et

al.[19] basically focused on ozone as a modulator of Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) and nuclear factor-κB (NFκB)NF-κB/Nrf2 pathways and IL-6 / IL-1β expression. They reported that with these molecular mechanisms, OT supported cytoprotective effects against tissue injury in many inflammatory diseases including viral infections.

The study by Thorp et al.[20] found that intravenous ozonated saline improved oxygenation of blood and tissues and lengthened an individual's ability to remain in a hypoxic environment. This study is a study supporting the potential benefit of adjuvant ozone therapy for COVID-19, similar to studies performed in China, Spain, Italy and South America.

A non-randomized pilot study by Schwartz et al.[21] performed complementary treatment with physiologic serum ozonation and reported that along with standard treatment it may be reliable for symptoms linked to COVID-19 disease in mild and severe patients and that no side effects were observed.

Angiotensin-converting enzyme 2 (ACE-2) is the entry receptor for COVID-19; the spike protein on the virus binds to an ACE-2 receptor on the cell surface and mediates viral fusion with the host cell and entry into the cell. This receptor is under control of Nrf2, regulating and blocking the activity of this receptor. As ozone causes rapid Nrf2 activation, this seems very likely to be an important physiological mechanism in blocking proliferation of endogenous COVID-19 virus by preventing contact with the receptor. Before treatment, 27 out of all health employee patients (50.9%) had positive PCR results, while no patient had positive PCR result after treatment ($p<0.001$) leading to consideration that rapid amelioration and return to work was related to the inability of the virus to enter the cell. At the same time, this effect is one of the benefits of administration of ozone therapy as prophylaxis.

Among 23 patients with positive CT results (4.5%), one was PCR negative before treatment and 22 (95.5%) were positive showing that patients had moderate and severe clinic and may worsen with rapid progression. The half past six day hospitalization duration of our health workers receiving ozone therapy is much shorter compared to the hospitalization durations reported in the literature, and their discharge in the early period is linked to receiving ozone therapy.

CONCLUSION

In conclusion, ozone therapy has begun to be included in treatment protocols as an important immunotherapy method especially to protect and treat health employees and to ensure a return to work in a short duration.

References

1. *Baki S, Piyal B. Work-Family Conflict as Regard to Healthcare Workers in Extraordinary Situations such as COVID -19 Pandemic Health and Community- 2020; July (Suppl) 119-123.*
2. *Pala SÇ, Metintaş S. Healthcare Workers in the COVID-19 Pandemic. ESTUDAM Journal of Public Health. 2020;5(COVID-19 Suppl.):156-168.*
3. *Saatçı E. COVID-19 Pandemic and Healthcare Workers: To Survive or To Live? Turkish Journal of Family Practice 2020; 24 (3):153-166.*
4. *S.F. Lumley, D. O'Donnell, N.E. Stoesser, P.C. Matthews, A. Howarth, et al. Eyre, for the Oxford University Hospitals Staff Testing Group. Antibody Status and Incidence of SARS-CoV-2 Infection in Health Care Workers NEJM 2020; December doi: 10.1056/NEJMoa2034545*
5. *Elvis AM, Ekta JS. Ozone therapy: A clinical review. J Nat Sci Biol Med. 2011 Jan;2(1):66-70. doi: 10.4103/0976-9668.82319.*
6. *Hernández A, Viñals M, Isidoro T, Vilás F. Potential Role of Oxygen-Ozone Therapy in Treatment of COVID-19 Pneumonia. Am J Case Rep. 2020 Aug 17;21:e925849. doi: 10.12659/AJCR.925849.*
7. *Smith NL, Wilson AL, Gandhi J, Vatsia S, Khan SA. Ozone therapy: an overview of pharmacodynamics, current research, and clinical utility. Med Gas Res. 2017;7:212-9.*
8. *Rowen RJ, Robins H, Carew K, Kamara MM, Jalloh MI. et al. Rapid resolution of hemorrhagic fever (Ebola) in Sierra Leone with Ozone therapy. Afr J Infect Dis. 2016; 10 (1): 49-54.*
9. *Zaky S,Kamel SE,Hassan MS,Sallam NA,Shahata MA,Helal SR,et al. Preliminary results of ozone therapy as a possible treatment for patients with chronic hepatitis C. J Altern Complement Med.2011;17(3):259-63.*
10. *Valdenassi L, Franzini M, Ricevuti G,Rinaldi L,Galoforo AC, Tirelli U. Potentialmechanisms by which the oxygen-ozone (O2–O3) therapy could contribute to the treatment against the coronavirus COVID-19. Eur Rev Med Pharmacol Sci. 2020; 24 (8): 4059-4061*
11. *Dhand, NK, Khatkar MS. Statulator: An online statistical calculator. Sample Size Calculator for Comparing Two Paired Proportions. 2014. Accessed 10 November 2020 at [http://statulator.com/SampleSize/ss2PP.html]*
12. *Arsham H.Two Dependent Proportions Testing [http://home.ubalt.edu/ntsbarsh/businessstat/otherapplets/pairedprop.htm], Accessed 05.11.2020.*
13. *Hotchkiss RS, Opal SM. Activating Immunity to Fight a Foe - A New Path. N Engl J Med. 2020 Mar 26;382(13):1270-1272.*
14. *Franzini M, Valdenassi L, Ricevuti G, et al. Oxygen-ozone (O2-O3) immunoceutical therapy for patients with COVID-19. Preliminary evidence reported International Immunopharmacology 2020; 88 November :106879 https://doi.org/10.1016/j.intimp.2020.106879*
15. *Menendez-Cepero S, Zamora Z, Hernandez F. Importance of the toxicological tests in the application and safety of ozone therapy. J Ozone Ther. 2018; 2(3). doi:10.7203/jo3t.2.3.2018.10009.*
16. *Rowen RJ. Ozone and oxidation therapies as a solution to the emerging crisis in infectious disease management: a review of current knowledge and experience. Med Gas Res. 2019 Oct-Dec;9(4):232237. doi: 10.4103/2045-9912.273962. PMID: 31898609.*
17. *Verbeek JH, Rajamaki B, Ijaz S, Sauni R, Toomey E, Blackwood B, Tikka C, Ruotsalainen JH, Kilinc Balci FS. Personal protective equipment for preventing highly infectious diseases due to exposure to contaminated body fluids in healthcare staff. Cochrane Database Syst Rev. 2020 May 15;5:CD011621. doi: 10.1002/14651858.CD011621.pub5.*
18. *Zheng Z, Dong M, Hu K. A preliminary evaluation on the efficacy of ozone therapy in the treatment of COVID-19. J Med Virol. 2020 May 21:10.1002/jmv.26040. doi: 10.1002/jmv.26040.*
19. *Martínez-Sánchez G, Schwartz A, Donna VD. Potential Cytoprotective Activity of Ozone Therapy in SARS-CoV-2/COVID-19. Antioxidants (Basel). 2020 May 6;9(5):389. doi:10.3390/antiox9050389.*
20. *Thorp JA, Hollonbeck SA, Viglione DD, Green PC, Hodge JR, et al. (2020) Novel therapy for COVID-19 does intravenous ozonated-saline affect blood and tissue oxygenation? J Gynecol Res Obstet. 2020; 6(2): 046-050. doi: 10.17352/jgro.000085*
21. *Schwartz A, Martínez-Sánchez G, de Lucía AM, Viana SM, Constanta AM. Complementary application of the ozonized saline solution in mild and severe patients with pneumonia COVID-19: A non-randomized pilot study. J Pharm Pharmacogn Res 2021; 9(2): 126–142.*