

Could ozone therapy be used to prevent COVID-19?

Kardelen GENCER-ATALAY¹ , Tulay SAHIN² 

¹Physical Medicine and Rehabilitation Department, School of Medicine, Marmara University, Pendik, Istanbul, Turkey

²Pain Medicine Clinic, Sisli Hamidiye Etfal Training and Research Hospital, Health Sciences University, Sisli, Istanbul, Turkey

Corresponding Author: Kardelen GENCER-ATALAY

E-mail: kardelengencer@gmail.com

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ABSTRACT

Objective: Ozone therapy has been shown to be beneficial in the prevention and treatment of various viral infections. This study aimed to investigate the beneficial effect of ozone therapy against coronavirus disease 2019 (COVID-19).

Patients and Methods: A total of 71 individuals who completed at least ten sessions of ozone therapy applied by the method of major autohemotherapy within the last six months were included and telephone call surveys were made.

Results: Two out of 71 participants were confirmed to have COVID-19. They both had mild symptoms and were discharged from the hospital in five days. None of the participants with contact or travel history was infected.

Conclusion: Ozone therapy could be preventive against COVID-19. It could be considered as an alternative, easy-to-apply, safe, and inexpensive method in the fight against COVID-19.

Keywords: Coronavirus, Ozone, Preventive Medicine

1. INTRODUCTION

The first cases of a new type of Coronavirus, later to be named coronavirus disease 2019 (COVID-19) by the World Health Organization, were reported in late December 2019, China [1,2]. Since then, it has infected 495.200.191 people and killed 6.167.271 people worldwide [3]. To date as of April 02, 2022, although, some potential drugs have been administered to the patients, there is no concrete evidence concerning the effectiveness and safety of the COVID-19 treatment [4,5]. These potential treatment options based on previous efficacy results in treating various other diseases such as malaria, rheumatoid arthritis, Middle East respiratory syndrome, severe acute respiratory syndrome, Ebola, influenza, and autoimmune diseases are included in the therapeutic guidelines [5]. Meanwhile, ozone has become a promising supportive treatment method, and clinical trials about its antiviral efficacy have already been started [4,6].

Ozone, as a triatomic oxygen molecule, is one of the most powerful oxidants. The medical ozone mixture of 1-5% ozone in 95-99% oxygen can be administered to the body by different methods [7,8]. Ozone therapy is a safe and inexpensive therapy,

and depending on the dose, its biochemical effects can last up to six months. These biochemical modulation effects are an increase in red blood cell oxygen release and endothelial nitric oxide production, improvement in mitochondrial oxygen consumption and energy generation, inflammatory response regulation, immune system modulation, and antioxidation status activation [7,9]. In addition to these well-documented in vivo effects, it has also been shown to inactivate some viruses directly by oxidizing membrane glycoproteins [7,8]. Thus, it is thought to be effective for the prevention and treatment of COVID-19 [10].

In recent years, ozone therapy has become a popular alternative method for chronic pain management of various diseases such as fibromyalgia, knee osteoarthritis, and rheumatic diseases [11-13]. As a result of this, many individuals had already received ozone therapy before the outbreak of COVID-19. This study aimed to investigate the beneficial effect of ozone therapy against COVID-19 in these individuals. It was hypothesized that

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at least ten sessions of ozone therapy received within six months decreased the prevalence and severity of COVID-19.

2. PATIENTS and METHODS

This cohort study was conducted between May 06, 2020, and May 16, 2020. Participants were selected by a retrospective analysis of the individuals who had received ozone therapy at the Pain Medicine Clinic, Sisli Hamidiye Etfal Training and Research Hospital, University of Health Sciences, Istanbul. The inclusion criteria were determined as the completion of at least ten sessions of ozone therapy applied by the method of major autohemotherapy in the last six months. Individuals who received ozone therapy locally or had fewer than ten sessions, and those who did not want to participate were excluded. Suspected and confirmed cases of COVID-19 were determined

according to the seventh edition of the Diagnosis and Treatment Guidelines for COVID-19 [14]. The study was approved by the Ethics Committee of University of Health Sciences, Sisli Hamidiye Etfal Training and Research Hospital (approval number 2761), and the Republic of Turkey Ministry of Health Scientific Research Platform. The protocol was registered to ClinicalTrials.gov (NCT04400006). Patient consent was obtained from all participants.

Data collection was performed by a physiatrist with the surveys that were taken from the individuals who fulfilled the criteria. The interviews were performed by telephone calls and took approximately thirty minutes during weekdays. The survey involved questions on age, gender, height, weight, occupation, comorbidities, and concurrent medications, in addition to a detailed query concerning COVID-19 (Table I).

Table I. The survey that was taken by all participants

Since the beginning of March 2020 have you ever;
had a contact or travel history related to COVID-19?
<input type="checkbox"/> No <input type="checkbox"/> Yes, I had a history of.....
had one or more symptoms listed below:
<input type="checkbox"/> No <input type="checkbox"/> throat sore <input type="checkbox"/> fever <input type="checkbox"/> cough <input type="checkbox"/> shortness of breath <input type="checkbox"/> diarrhea <input type="checkbox"/> others.....
if yes,
How long have the symptoms lasted?
.....
Have you needed medical assistance?
<input type="checkbox"/> No <input type="checkbox"/> Yes, I went to.....
Have you received radiologic imaging?
<input type="checkbox"/> No <input type="checkbox"/> Yes, I received.....resulted.....
Have you tested for COVID-19?
<input type="checkbox"/> No <input type="checkbox"/> Yes, The name of the test was.....resulted <input type="checkbox"/> Positive <input type="checkbox"/> Negative
diagnosed with COVID-19?
<input type="checkbox"/> No <input type="checkbox"/> Yes
if yes,
Have you hospitalized?
<input type="checkbox"/> No <input type="checkbox"/> Yes
Which medicines have you used?
.....
Have you needed oxygenation or intensive care support?
<input type="checkbox"/> No <input type="checkbox"/> Yes.....

The major autohemotherapy procedure for all the participants was applied as follows [7]: 100mL of blood was drawn by a vacuum from the antecubital vein into a sterile glass bottle in which 12 mL of 3.13% sodium citrate solution was included as an anticoagulant (MediPac®, Germany). A corresponding volume (100mL) of gas with an ozone concentration of 10-20 µg/mL was

immediately added and continuously mixed by a gentle rotating movement to avoid foaming in the blood in the bottle. Ozone was produced by a Blue-S medical ozone generator (Turkozone®, Turkey). Reinfusion was accomplished in about 15-20 minutes, and the whole procedure was carried out in approximately 30 minutes and was repeated two or three times a week.

Statistical Analysis

Statistical analysis was performed with a statistical software package (SPSS for Windows, version 18.0, SPSS). Demographic characteristics and clinical and therapeutic features of the study population were described as the mean value and standard deviation, or as the median and range, and the number and percentage. The prevalence of COVID-19 in the study population was calculated.

3. RESULTS

A total of 74 individuals who completed at least ten sessions of ozone therapy applied by the method of major autohemotherapy within the last six months were assessed for eligibility. Of these, three of them did not want to participate; thus, 71 of them agreed to take the telephone call surveys and were included in the study. The demographic characteristics and clinical features of the participants are shown in Table II, and details of the ozone therapy administration are displayed in Table III.

Table II. Participant characteristics and clinical features

Age (years)	50.97±12.07	
30-39	13	(18.3)
40-49	22	(31)
50-59	18	(25.4)
60-69	13	(18.3)
70-79	4	(5.6)
80-90	1	(1.4)
Gender		
Female	46	(64.8)
Male	25	(35.2)
BMI (kg/m²)	25.4±3.94	
Normal (18.5-24.9)	35	(49.3)
Overweight (25-29.9)	24	(33.8)
Obese (30-34.9)	9	(12.7)
Extremely obese (>35)	3	(4.2)
Occupation		
Medical professional	11	(15.5)
Other white-collar employee	14	(19.7)
Blue-collar employee	9	(12.7)
Housewife	20	(28.2)
Retiree	17	(23.9)
Comorbidity		
None	34	(47.9)
Hypertension	7	(9.9)
Diabetes Mellitus	5	(7)
Thyroid disease	4	(5.6)
Cancer	2	(2.8)
Chronic Respiratory disease	2	(2.8)
Coronary artery disease	1	(1.4)
Cerebrovascular disease	1	(1.4)
Rheumatologic disease	1	(1.4)
Multiple	14	(19.7)

Data= Mean±SD, n(%), BMI= Body mass index

Twenty-two of the participants had histories of either contact with a COVID-19 infected person or of international travel. Of these, 10 of them were medical professionals who actively worked during the pandemic period. Two medical professionals and two others with contact or travel history showed clinical symptoms that did not last more than a week. Their thorax computed tomography did not reveal an abnormality, and real-time polymerase chain reaction (PCR) test for COVID-19 were negative. Eighteen participants with contact or travel history had no clinical symptoms. Forty-six of the participants did not have contact or travel history, or any clinical symptoms. Besides this, three of the participants without contact or travel history had clinical symptoms and needed medical assistance. COVID-19 was confirmed in two of them. One was a 61-year old retired male who had a history of asthma and gout, and the other one was a 41-year old obese female without any comorbidities. They were both hospitalized and received combinations of hydroxychloroquine, oseltamivir, or azithromycin. They had only mild symptoms and were discharged in five days. None of the participants other than these two had received any specific medication against COVID-19 (Table IV). None of the patients had severe symptoms, and the prevalence of COVID-19 in the study population was found to be 2.8%.

Table III. Details of ozone therapy applied by the method of major autohemotherapy

Indication		
Pain		
Chronic widespread pain	28	(39.4%)
Musculoskeletal pain	21	(29.6%)
Fatigue	10	(14.1%)
Other	12	(16.9%)
Total number of sessions	10	(10-22)
Dose of each session (µg/mL)	15	(10-20)
The time from the last session of ozone therapy to the survey was taken (days)		
0-29	20	(28.2%)
30-59	20	(28.2%)
60-89	15	(21.2%)
90-119	7	(9.9%)
120-149	3	(4.2%)
150-179	6	(8.5%)

Data= n(%), Median(Min-Max)

Table IV. The results of the survey that was taken by all participants

Case No	Contact or travel history	Clinical manifestations	Radiological evidence	RT-PCR Test	
1	-	+	+	+	A 61-year old male who had a history of asthma and gout was administered to hospital with complaints of throat sore, myalgia, and fatigue. Bilateral multiple subpleural ground-glass densities were detected in thorax CT. He was given a combination of hydroxychloroquine and oseltamivir. He had mild symptoms, did not need oxygen supplementation.
2	-	+	+	+	A 41-year old obese housewife who referred from primary care physician had symptoms of fever, cough, and dyspnea. Atypical pneumonia findings were confirmed with thorax CT. She was given a combination of hydroxychloroquine, oseltamivir, and azithromycin. She had mild symptoms, did not need oxygen supplementation.
3	+	-	NA	NA	Medical professionals, aged between 31 years and 58 years, actively worked against COVID-19. One of them had a malignancy history and another one had thyroid disease.
...					
10					
11	+	+	-	-	Two medical professionals actively worked against COVID-19. A 30-year old male without a history of comorbidities had fever, cough, and dyspnea symptoms for a few days. Another 34-year old female with asthma had a complaint of shortness of breath for a week.
12					
13	+	-	NA	NA	Individuals aged between 39 years and 60 years. Two of them had hypertension, and one had a malignancy history.
...					
22					
23	+	+	-	-	A 40-year male had fever for two days, and a 37-year old female complained about cough for several days.
24					
25	-	+	NA	-	A 30-year old female complained from shortness of breath for more than a few weeks.
26	-	-	NA	NA	Individuals aged between 36 years and 86 years
...					
71					

4. DISCUSSION

In this study, the surveys taken on seventy-one individuals who had completed at least ten sessions of ozone therapy within the last six months were analyzed, and it was revealed that none of the participants with contact or travel history were infected. Besides, it was shown that 45.4% of participants with contact or travel history were medical professionals who worked actively during the pandemic period, and even though two had nonspecific mild clinical symptoms, none of them were diagnosed with COVID-19. Another noteworthy finding was that the two persons in the high-risk category for COVID-19 recovered from the disease quite mildly. These results support the idea of the preventive effect of ozone therapy against COVID-19, and the hypothesis of at least ten sessions of ozone therapy received within six months decreased the severity of COVID-19.

The research and meta-analyses have emphasized that being over the age of 50 years, obesity, and comorbidities such as hypertension, diabetes mellitus, chronic respiratory disease, coronary artery disease, or cerebrovascular disease were the

high-risk factors for COVID-19 [15-20]. In this study, it was discerned that 50.7% of the study population was over the age of 50 years, while 16.9% were obese or extremely obese, and 52.1% had comorbidity, 19.7% of these had multiple comorbidities. If these are considered all together, it could be easily concluded that the study population was at a higher risk than the normal population. Therefore, the prevalence of COVID-19 in the study population could be found to be higher than the general population of Turkey [3].

The possible preventive and antiviral effects of ozone therapy against COVID-19 could be through various mechanisms. The preventive effect could be the oxidative stress created by ozone in the body to stimulate the peripheral phagocytic cells, activate the antioxidant system, and restore the immune system [21]. The antiviral effect could be the peroxidation occurred by ozone to damage the viral capsule and disrupt the reproductive cycle or fusion of the virus [22]. In addition, particularly for Coronavirus, ozone therapy could disturb the virus-cell interaction by Nrf2 activation and restrain the inflammatory process by NFkB inhibition [23]. Moreover, it is considered to reduce ischemia-reperfusion injury, which causes the multi-organ dysfunction

in the advanced disease period [24]. Ozone therapy has been reported to be beneficial in various viral infections including COVID-19 [25-28]. The optimal ozone therapy dose required to provide these effects against COVID-19 remains unknown [29]. This study could only indicate that ten sessions of low-medium dose ozone therapy within the previous six months prevented COVID-19. There is still a need for future studies that investigate its usage or optimal doses for treatment.

The limitations of the study, as a consequence of not being designed before the outbreak of COVID-19, could be listed as the lack of a control group and the relatively low number of participants. Besides, the design of the study could have caused memory bias. Lastly, variational antioxidant capacities, lifestyle habits, and the COVID-19 contact duration of the participants could have confounded the findings of the study. However, drawing attention to the preventive effect of ozone therapy against COVID-19 for the first time could be one of the strengths of the study.

In conclusion, none of the individuals who completed at least ten sessions of ozone therapy within the last six months with contact or travel history was infected, and even though two of them in the high-risk category were diagnosed with COVID-19, they recovered in a short time without complications. These results support the fact that ozone therapy could be preventive against COVID-19. Ozone therapy, as an easy-to-apply, safe, and inexpensive method, should be considered to deploy worldwide in the warfare of COVID-19.

Compliance with Ethical Standards

Ethical approval: The study was approved by the Ethics Committee of University of Health Sciences, Sisli Hamidiye Etfal Training and Research Hospital (approval number 2761), and the Republic of Turkey Ministry of Health Scientific Research Platform. The protocol was registered to ClinicalTrials.gov (NCT04400006). Patient consent was obtained from all participants.

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