Effectiveness of ozone therapy in addition to conventional treatment on mortality in patients with COVID-19

Şahin Çolak[1], burcu genç yavuz[2], Mürsel Yavuz[3], Burak Özçelik[4], Metin Öner[4], Asu Özgültekin[4], and Seniha Şenbayrak[5]

[1]University of Health Sciences Haydarpasa Numune Training And Research Hospital
[2]University of Health Sciences, Haydarpasa Numune Training and Research Center
[3]Kosuyolu Rezonans Clinic
[4]University of Health Sciences, Haydarpasa Numune Training and Research Hospital
[5]Department of Infectious Diseases and Clinical Microbiology, Health Sciences University, Haydarpasa Numune Training and Research Hospital

December 12, 2020

Abstract

Aim In this study, we aimed to investigate the effectiveness of ozone therapy, which is one of the integrative medicine applications that has been used safely for many years, on the prevalence of mortality in patients receiving COVID-19 treatment. Methods This was a prospective, controlled study conducted on patients with COVID-19 who were hospitalized in Health Sciences University, Haydarpasa Numune Training and Research Hospital. In this study, 55 patients were included. The patients were divided into two groups as the ozone group and the control group. Ozone therapy (major autohemotherapy) was applied to 37 patients who were being treated with the appropriate COVID-19 treatment protocol determined by the infectious diseases committee of our hospital. The ozone treatment protocol consisted of seven sessions (1 session/day) of intravenous ozone administration, applied in a volume of 100 mL and a concentration of 30 µg/mL. Only the conventional COVID-19 treatment protocol was applied to 18 patients in the control group. Clinical follow-up was performed until the discharge of the patients from the hospital with successful treatment or until the mortality occurred. Factors affecting mortality were analyzed using univariate regression analysis. Results Intensive care unit (ICU) hospitalization was required in six of 37 patients who were treated with ozone (16.2%), while four of 18 patients in the control group required ICU treatment (22.2%) (p = 0.713). When the mortality rates between the two groups were compared, mortality was lower in the ozone group (p = 0.032). As a result of univariate logistic regression analysis performed to determine the factors affecting mortality, treatment without ozone therapy was determined as a risk factor for mortality (OR:0.149, 95%CI 0.026-0.863, p=0.034). Conclusion In this study, we demonstrated that administration of ozone therapy along with the conventional medical treatment in patients hospitalized for COVID-19 could reduce mortality.

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Intensive care unit (ICU) hospitalization was required in six of 37 patients who were treated with ozone (16.2%), while four of 18 patients in the control group required ICU treatment (22.2%) (p = 0.713). When the mortality rates between the two groups were compared, mortality was lower in the ozone group (p = 0.032). As a result of univariate logistic regression analysis performed to determine the factors affecting mortality, treatment without ozone therapy was determined as a risk factor for mortality (OR:0.149, 95%CI 0.026-0.863, p=0.034).

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Key Words: Ozone therapy, Covid-19, Mortality

INTRODUCTION

The COVID-19 outbreak that began at the end of 2019 continues to affect the whole world. Although there was a decrease in the severity of the pandemic in the summer of 2020, the increase in the number of cases with the arrival of autumn made the whole world uneasy again. SARS-CoV-2 is transmitted from person to person via droplets or direct contact and the most common symptoms presented during the prodromal phase are fever, dry cough, myalgia and fatigue [1,2]. Although the cases can be asymptomatic or have mild symptoms, it has also been reported that approximately 20% of the hospitalized patients who have a more severe clinical presentation further develop acute respiratory distress syndrome (ARDS) [3,4]. The leading causes of death due to the virus are respiratory failure, hyperinflammation, cytokine storm, or multiorgan failure [5].

There is no specific antiviral drug approved by the US Food and Drug Administration (FDA) or European Medicines Agency (EMA) in the treatment of COVID-19. WHO also shares the opinion that a specific treatment still does not exist [6]. Since an effective and specific treatment for SARS-CoV-2 has not been developed yet, interest in supportive treatments with proven safety, such as vitamin D supplementation, has increased to prevent mortality and morbidity in the management of the disease [4].

Ozone therapy has been known for more than 150 years[7]. Its effectiveness, particularly in the treatment of infectious diseases, has been demonstrated in many studies conducted in Cuba, Italy, Germany, Russia and Spain [5]. The bactericidal, fungicidal and virucidal effects of ozone have been demonstrated in various studies[5]. This strong antimicrobial effect has also enabled ozone to be widely used as a water disinfection agent [7]. Ozone has been reported to be helpful in the treatment of viral diseases by inducing the release of antiviral cytokines such as IFN and by the modulation of pro-inflammatory cytokines release, such as IL-6, thanks to its direct oxidation effect [5,8]. Besides, ozone provides oxygen substantially to tissues with poor oxygenation [6,9].

In this study, we investigated the effectiveness of ozone therapy to reduce mortality rates in patients hospitalized due to COVID 19.

Materials and Methods

Study population and data collection

This study was approved by the Ethical Committee of the University of Health Sciences Haydarpasa Numune Training and Research Hospital and conducted following the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients or their legal representatives. We performed a prospective quasi-experimental before-and-after pilot study. This study included mild and severe COVID-19 patients hospitalized in the Haydarpasa Numune Training and Research Hospital, with lung involvement and RT-PCR (reverse transcriptase-polymerase chain reaction) positiveness for SARS-CoV-2.

The required sample size of this study was calculated using the Gpower 3.1 [10]. Based on the literature [4], a sample size of 51 patients was required to provide 80% power with 5% alpha and effect size w =0.394. The participants were randomly assigned in a 2:1 allocation to the control (n:18) and treatment (n:37) groups using a computer-generated randomization.

Thirty-seven patients who met the following criteria were included in the ozone group of our study. Inclusion criteria were as follows: application to the emergency department with fever and respiratory system complaints, being 18 years or older, lung tomography findings indicating COVID-19 in accordance with the literature[11-13], positivity for SARS-CoV-2 nucleic acid (RT-PCR) test, acceptance of ozone therapy (by the patient or his/her legal guardian) by written consent. Patients who were breastfeeding, pregnant or patients with a diagnosis of glucose 6-phosphate dehydrogenase (G-6PD) deficiency were excluded from this study.

For the control group, 18 patients were included who met the above-mentioned inclusion criteria but did not consent to the ozone treatment protocol and accepted to participate in the study in the control group by giving written consent. Leucocyte and lymphocyte count, ferritin, D-Dimer, procalcitonin, CRP, and IL-6 measurement tests were performed at the time of admission among patients with findings consistent with COVID-19 in lung tomography, and then patients were hospitalized.

Procedures

Patients in the ozone and control groups received the appropriate medical treatment according to the COVID-19 protocol determined by the infectious diseases committee of our hospital and according to their individual clinical status. The main drugs in this treatment protocol consisted of hydroxychloroquine (400 mg every 12 hours on the first day, 200 mg every 12 hours for the next four days), enoxaparin, favipiravir, antibiotics if a secondary bacterial infection is considered and antipyretics if required. Other symptomatic treatment measures were also taken according to the patient's clinical picture. Ozone Major Autohemotherapy (MAH) was applied to the ozone patient group, along with the conventional medical treatment that was deemed appropriate. Ozone was produced by the Turkozone Blue S CE medical device. The ozone bottle and set were disposable, made of medical-grade materials, and fully ozone compatible (Medipac Medical®, Germany and Bexen Medical®, Spain).

MAH was administered to the patients once daily for seven consecutive days. Each time, 100 ml of venous blood was collected and mixed with O3 gas at the 1:1 ratio of oxygen-ozone to blood volume, with the final concentration of oxygen-ozone being 30µg/ml.

Patients were followed up until they were discharged from the hospital or mortality occurred. In our study, the pre-treatment biochemical test results of the patients were compared and the mortality rate observed in the groups was calculated. The discharge and mortality rates of the patients in the control group and the patients in the ozone group were compared.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY). The normality assessment was performed using the Shapiro–Wilk test. Descriptive analyses were presented using mean±SD (range), median (range), or n (%), where appropriate. Categorical data were analyzed using the Pearson chi-square test and Fisher's Exact test. Mann–Whitney U test and Student's t-test were utilized for analysis of non-normally and normally distributed numerical data, respectively. Wilcoxon Signed Ranks test was used to compare the measured parameters of patients before and after the treatment. Univariate and multivariate logistic regression analysis was used to determine independent risk factors associated with mortality. The variables with $p<0.1$ in the univariate analyses were further tested in the multivariate models. Odds ratio (OR) with corresponding 95% confidence intervals (95% CIs) was reported. A p-value of less than 0.05 was considered statistically significant.

RESULTS

In this study, 55 patients diagnosed with COVID-19 pneumonia and hospitalized were included. The mean age of the patients was 60,2±14,8 (min:25, max:88) and 52.7% (n=29) of the participants were male. The mean age of the patients in the group in which ozone therapy was not applied (n = 18) was 64.7 ± 10.4, while the mean age of the patients in the ozone group (n = 37) was 58.03 ± 16.3. While 44.4% of the patients in the group that did not receive ozone treatment were females, 48.6% of the patients in the ozone group were women. Mean age (p = 0.118) and gender distribution (p = 0.769) of the patients according to the patient groups were similar (Table 1).

When the distribution of patients in both groups for comorbidity was compared, there was no significant difference concerning diabetes mellitus (DM) (p = 0.713), hypertension (p = 0.925), congestive heart failure (CHF) (p = 0.999), coronary artery disease (CAD) (p = 0.346) and neoplasms (p = 0.590). However, chronic renal failure (CRF) (p = 0.043) was observed with a higher rate in patients receiving ozone therapy (Table 1). Although the rate of chronic obstructive pulmonary disease (COPD) was observed to be higher in patients who received ozone therapy, this difference was not statistically significant (p = 0.078). When the vital signs of the patients during the admission to the hospital were evaluated, no significant difference was found between the groups concerning body temperature (p = 0.619), heart rate (p = 0.109), systolic blood pressure (p = 0.663) and saturation of O2 (p = 0.068). There was no difference in pre-treatment levels of IL-6 (p = 0.993), D-Dimer (p = 0.167), ferritin (p = 0.893) and procalcitonin (p = 0.352) according to the study groups. The rate of hospitalization in the intensive care unit was similar according to the study groups (p = 0.713) (Table 1).

In our study, it was determined that the mortality rate in the ozone group was significantly lower than the control group (p = 0.032). When all participants were evaluated, the mortality rate was 50% in patients hospitalized in the intensive care unit and 4.4% in patients hospitalized in the regular ward. The mortality rate was higher in patients hospitalized in the intensive care unit (p = 0.001). In the group of patients who did not receive ozone treatment (n = 18), the mortality rate of the patients hospitalized in the intensive care unit (75%) was higher than the patients followed up in the regular ward (14.3%) (p = 0.044). Similarly, in the group that received ozone therapy (n = 37), the mortality rate in patients requiring intensive care (33.3%) was higher than in patients followed up in the ward (0%) (p = 0.023). When the mortality rates of patients who were hospitalized in intensive care (n = 10) were compared concerning the treatment groups, it was observed that the mortality rate of patients who received ozone therapy (33.3%) was lower than patients who did not (75%), while this difference was not statistically significant (p = 0.524). Among the patients treated in the ward (n = 45), all the 31 patients who received ozone therapy were discharged after successful treatment, while mortality occurred in 6.1% of 14 patients who did not receive ozone therapy. Although there was no significant difference between the death rates of the patients hospitalized in the regular ward concerning the treatment groups (p = 0.092), there was no death in the ozone group.

Ozone therapy was found effective in the univariate regression analysis performed to determine the factors affecting mortality (OR: 0.149; %95 CI: 0.026-0.863; p=0.034) (Table 2).

Discussion

In our study, we applied ozone therapy to patients infected with SARS-Cov-2 in addition to conventional treatment and investigated the clinical outcomes of the patients compared to the group that did not receive ozone therapy. When we compared the results in the two groups that were similar regarding age, gender, and comorbid diseases, we found that the mortality rate was significantly lower in the ozone treatment group. In the univariate regression analysis of factors affecting mortality, the findings suggest the effectiveness of ozone therapy in COVID-19 treatment.

The specific treatment of COVID-19 has not been developed yet, but the fight against coronavirus with antiviral drugs and symptomatic treatments goes on worldwide. In vaccine studies, no one has yet achieved a definite success so far. The development of alternative treatments to reduce the mortality of COVID-19 continues. In addition, ozone therapy, known for its high oxidant properties, is a method of treatment that has been used safely in many countries in infectious, immunological and vascular diseases for many years [14]. SARS-CoV-2 is an enveloped virus and the high density of double-bonded molecular bodies in the structure of it, which facilitates such oxidant agents to damage the integrity of the virus [6,15]. Similar to the Ebola Virus, the spike and envelope proteins of SARS-CoV-2 are rich in cysteine and tryptophan amino acids, which make them vulnerable to oxidation [16,17]. Ozone therapy thus causes oxidation in the cysteine and tryptophan residues of the viral membrane proteins [15,18]. Apart from the strong oxidant effect, it has also been reported that lymphocytes and monocytes re-infused into the patient during MAH would stimulate the immune system[6]. Thus, viral replication and the progression of infection can be prevented [19,20]. The Menendez Cuban group reported in their animal studies that the previously applied ozone therapy to the endotoxic shock model was as effective as dexamethasone treatment in reducing Tumor Necrosis Factor α levels[21,22]. This information suggests that ozone therapy is quite valuable in preventing a cytokine storm, one of the leading causes of death in patients infected with COVID-19 [22-25]. In our study, we applied ozone therapy to hospitalized COVID-19 patients. We found that the mortality rate in ward and intensive care patients in the group receiving ozone therapy was significantly lower than the control group who did not receive ozone therapy ($p = 0.032$).

Many studies have reported that advanced age and comorbid diseases may negatively affect the prognosis of COVID-19 and increase mortality[26]. Diabetes, hypertension, cardiovascular disease, chronic respiratory disease, cancer and cerebrovascular disease are mainly known risk factors in this respect [26,27]. It has also been reported that acute kidney injury (AKI) may develop during the course of patients infected with COVID-19, and this situation may significantly increase the risk of mortality [28,29]. The development of AKI also may lead to a poor prognosis in patients who are infected with COVID-19 with chronic kidney failure (CRF) or with a history of renal transplant [28]. In a study conducted on 101 cases that died due to COVID-19, it was reported that 11% of the patients had CRF and 23% developed AKI [30]. In our study, we could not find any significant difference between the groups concerning DM, HT, CAD, COPD, congestive heart failure, or neoplasm rates. At the same time, although 21.6% of patients in the ozone group had a history of CRF ($p = 0.043$), a lower mortality rate was observed compared to the other group. We think this finding supports the effectiveness of ozone therapy.

Another prognostic factor in patients with COVID-19 is the elevation of D dimer, Ferritin, and Interleukin-6 levels. These parameters were associated with poor prognosis in many studies [31,32]. In our study, no significant difference was found between the groups in prognostic factors, such as IL-6, D-Dimer, and Ferritin levels (Table 1).

In COVID-19, for which a specific treatment is not yet available, clinical management sometimes challenges both physicians and patients. Not every patient gives the same response to every drug. At the same time, the toxic side effects of the drugs used may negatively affect the course of the disease. Ozone therapy, on the other hand, is an inexpensive, reliable, and well-known method of treatment for many years. In our study, no side effects that could be associated with ozone treatment were observed in the group which received it. We consider that mortality rates can be further decreased with ozone therapy to be applied in addition to the existing conventional treatment modalities.

The limitations of our study are that this study was conducted in a single-center, and the number of patients

was small. Multi-center studies to be conducted on a larger patient population will further provide valuable insights into the understanding of the effectiveness and significance of ozone therapy.

Conclusion

In conclusion, in this study, we demonstrated that applying ozone therapy to patients hospitalized for COVID-19 could contribute to clinical outcomes. No side effects related to ozone therapy were observed in our study. At the same time, the positive effects of ozone on the control of oxidative stress and immunomodulation have been supported by decreasing mortality rates and univariate regression analysis.

Acknowledgment Funding

The authors did not apply for a specific grant for this research from any funding agency in the public, commercial or non-profit sectors.

Competing Interests

Authors declare no conflict of interest.

Table 1. Comparison of the control group and ozone group, regarding age, gender, comorbidities, temperature, pulse, systolic blood pressure, Saturasyon O_2 and laboratory parameters based on the in-hospital mortality

	Control Group (n:18)	**Control Group (n:18)**	**Ozone Group (n:37)**	**P**
Age min-max mean± sd	42.0-83.0 64,7±10,4	42.0-83.0 64,7±10,4	25.0-88.0 58,03±16,3	0,118
Gender				
male	10(55,6)	10(55,6)	19(51,4)	0,769
Female	8(44,4)	8(44,4)	18(48,6)	
Co-morbidities				
Diabetes	4(22,2)	4(22,2)	6(16,2)	0,713
Hypertension	9(50)	9(50)	19(51,4)	0,925
Coronary artery disease	3(16,7)	3(16,7)	11(29,7)	0,346
COPD	1(5,6)	1(5,6)	11(29,7)	0,078
Congestive heart failure	1(5,6)	1(5,6)	4(10,8)	0,999
Neoplastic disease	2(11,1)	2(11,1)	2(5,4)	0,590
Chronic renal failure	0(0)	0(0)	8(21,6)	**0,043**
Temperature °C (med, min-max)	36,65(36-38)	36,65(36-38)	36,5(36-38,3)	0,619
Pulse bpm (med, min-max)	90,78±9,97(74-108)	90,78±9,97(74-108)	86,46±8,86(72-110)	0,109
SBP mmHg (med, min-max)	129,5±22,54(93-170)	129,5±22,54(93-170)	132,35±22,65(90-181)	0,663
LC (med, min-max)	LC (med, min-max)	95(80-99)	93(82-99)	0,068
IL-6 pg/mL	19,05(3,5-69)	19,05(3,5-69)	17,5(2,84-87,5)	0,993
D-Dimer ng/mL	785(240-10190)	785(240-10190)	1165(417-7504)	0,167
Ferritin ng/mL	234,5(95-1165)	234,5(95-1165)	334(6-2907)	0,893
Procalcitonin ng/mL	0,05(0,05-16)	0,05(0,05-16)	0,05(0,05-3,39)	0,352

	Control Group (n:18)	**Control Group (n:18)**	**Ozone Group (n:37)**	**P**
Intensive care unit	4(22,2)	4(22,2)	6(16,2)	0,713
Mortality	5(27,8)	5(27,8)	2(5,4)	**0,032**

Abbreviations: COPD, chronic obstructive pulmonary disease; SBP, Systolic Blood Pressure, LC; Laboratory characteristics. Data are presented as mean±SD (range), median (range) or n (%). Student's t test, Mann-Whitney U test, Pearson chi-square test, Fisher's Exact test.

Table 2. Univariate regression analysis of factors affecting mortality

	Univariate Model	**Univariate Model**
Variables	**OR (95%CI)**	**p**
Age	1,059(0,990-1,133)	0,098
Male	0,635(0,128-3,146)	0,578
Diabetes	4,393(0,804-23,999)	0,088
Hypertension	1,333(0,269-6,606)	0,725
CAD	1,2(0,205-7,011)	0,840
COPD	1,52(0,256-9,028)	0,645
CHF	1,833(0,175-19,252)	0,613
CRF	2,8(0,440-17,799)	0,275
Temperature	0,42(0,070-2,532)	0,344
Pulse	1,046(0,963-1,136)	0,286
SBP	0,985(0,949-1,023)	0,438
Saturasyon O_2	1,017(0,849-1,219)	0,851
Ozone therapy	0,149(0,026-0,863)	**0,034**

Abbreviations: CAD, Coronary artery disease; CHF, Congestive heart failure; COPD, chronic obstructive pulmonary disease; CRF, Chronic renal failure; SBP, Systolic Blood Pressure; CI, confidence interval; OR, odds ratio

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