

OZONE THERAPY USE AS A COMPLEMENTARY SUPPORT IN TREATMENT OF ICU COVID-19 PATIENTS

Cernei N.^{1,2}, Baltaga R.^{1,2}, Civirjic I.^{1,2}, Arnaut O.^{1,3}, Moghildea V.^{1,2}, Sandru S.^{1,2}

¹ Chair of anesthesiology and reanimatology no. 1 "Valeriu Ghereg", Nicolae Testemitanu State University of Medicine and Pharmacy, Chisinau, Republic of Moldova

² Department of anesthesia and intensive care, Institute of Emergency Medicine, Chisinau, Republic of Moldova

³ Chair of human physiology and biophysics, Nicolae Testemitanu State University of Medicine and Pharmacy, Chisinau, Republic of Moldova

Work was done in Department of Anesthesia and Intensive Care, Institute of Emergency Medicine, Toma Ciorba str., Chisinau, Republic of Moldova

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ВИКОРИСТАННЯ ОЗОНОТЕРАПІЇ ЯК ДОДАТКОВОЇ ПІДТРИМКИ ПРИ ЛІКУВАННІ ХВОРИХ НА COVID-19 У ВІДДІЛЕННІ ІНТЕНСИВНОЇ ТЕРАПІЇ

Черней Н., Балтага Р., Цивіржик І., Арнаут О., Могілдея В., Шандру С.

Вступ і цілі: досі немає конкретних стратегій лікування, окрім підтримуючого лікування величезної кількості летальних випадків пандемії COVID-19. Використання газу озону (ОЗ) як терапії в альтернативній медицині викликало скептицизм через його нестабільну молекулярну структуру. Сьогодні ми можемо твердо стверджувати, що озон здатний модулювати запалення, діючи на «цитокіновий шторм», зменшувати гіпоксію тканин, зменшувати гіперкоагуляцію та порушення реплікації вірусу. Через багато невизначеностей щодо лікування COVID-19 виник великий інтерес до потенційної ролі ад'ювантної озонотерапії, яка може дуже добре доповнювати стандартну терапію COVID-19. Широкий спектр втручань, включаючи противірусні препарати, імуномодулятори, реконвалесцентну плазму та фітотерапію, не були підтверджені як ефективні проти SARS-CoV2. Метою цього дослідження було оцінити вплив озонотерапії на перебіг хворих на COVID-19.

Матеріали та методи: проспективне рандомізоване клінічне дослідження типу «випадок-контроль», яке включало 100 пацієнтів з Covid-19 із пневмонією середнього ступеня тяжкості, які були госпіталізовані у відділення інтенсивної терапії в період з липня 2020 року по лютий 2021 року, розділених випадковим чином на дві групи. Дослідницька група з 50 пацієнтів отримувала стандартне лікування та озонову аутогемотерапію (ОЗ-АНТ) один раз на день протягом семи днів поспіль. Озонова аутогемотерапія передбачала введення 150 мл аутологічної цільної крові, збагаченої 150 мл киснево-озонової суміші з концентрацією озону 40 мкг/мл. Контрольну групу склали 50 пацієнтів, які отримували стандартне лікування згідно зі стаціонарним протоколом. Були проаналізовані первинні результати (смертність) і вторинні результати (тривалість неінвазивної вентиляції легенів, тривалість перебування у відділенні інтенсивної терапії та госпіталізації, шкала Brixia на 1-й і 7-й день озонотерапії та співвідношення P/F на 1-й і 7-й день озонотерапії).

Результати: Смертність у контрольній групі порівняно з групою дослідження становила 34% (ДІ95% 22,1, 47,7) проти 26% (ДІ95% 15,4, 39,3) без статистичної значущості ($p = 0,513$). Вторинний результат, такий як тривалість перебування у відділенні інтенсивної терапії та лікарні, не показав жодної статистичної значущості серед досліджуваних груп. Співвідношення P/F на 7-й день озонотерапії було вищим у групі дослідження 287 (IQR 150) проти 210 (180,75) зі статистичною значущістю ($p=0,007$). Оцінка Brixia на 7-й день озонотерапії була нижчою в групі дослідження 8 (IQR-5) проти 9 (IQR – 7) ($p=0,037$).

Висновок: у цьому дослідженні було продемонстровано, що застосування озонотерапії, як додаткова підтримка госпіталізованих пацієнтів з COVID-19, не впливає на смертність. Водночас спостерігався позитивний вплив озону на покращення співвідношення P/F та оцінки Brixia на сьомий день озонотерапії. У нашому дослідженні не було виявлено жодних побічних ефектів, пов'язаних із озонотерапією.

Ключові слова: озонотерапія, SARS-CoV-2, пандемія, аутогемотерапія, COVID-19.

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Introduction and objectives: There is still no specific treatment strategies aside from supportive management of huge amount of fatal Pandemic COVID-19 cases. The use of ozone (O₃) gas as a therapy in alternative medicine has attracted skepticism due to its unstable molecular structure. Today we can affirm strongly that ozone is capable to modulate inflammation acting on the “cytokine storm”, to reduce tissue hypoxia, to decrease hypercoagulability and impaired viral replication. Due to many uncertainties around the management of COVID-19, there has been lots of interest in the potential role of adjuvant ozone therapies that can very well complement the standard COVID-19 therapy. A wide range of interventions, including antiviral medications, immunomodulators, convalescent plasma, and herbal medicinal therapy were not confirmed as effective against SARS-CoV2. The goal of this research was evaluation of the influence of ozone therapy on COVID-19 patients outcome.

Materials and methods: A prospective randomized case-control clinical study, including a number of 100 Covid-19 patients with moderate pneumonia admitted in ICU between July 2020-February 2021 divided random in two groups. Study group with 50 patients, receive standard treatment and ozone autohemotherapy (O₃-AHT) once daily for seven days consecutive. Ozone autohemotherapy involved administration of 150 ml autologous whole blood enriched with 150 ml of oxygen-ozone mixture with a 40 µg/mL ozone concentration. Control group included 50 patients, receive standard treatment according to the institutional protocol. Were analyzed primary outcome (mortality) and secondary outcomes (non-invasive ventilation duration, ICU and hospital length of stay, Brixia score at 1st and 7th day of ozone therapy and P/F ratio at 1st and 7th day of ozone therapy).

Results: The mortality in control group versus study group was 34% (CI95% 22.1, 47.7) vs. 26% (CI95% 15.4, 39.3) without statistical significance ($p = 0.513$). The secondary outcome like length of stay in ICU and hospital, did not show any statistical significance among the examined groups. The P/F ratio on day 7 of ozone

therapy was higher in study group 287 (IQR 150) vs 210 (180.75) with statistical significance ($p=0.007$). Brixia score at day 7th of ozone therapy was lower in study group 8 (IQR-5) vs 9 (IQR - 7) ($p= 0.037$).

Conclusion: In this study, was demonstrated that application of ozone therapy, like a complimentary support to COVID-19 hospitalized patients does not influence the mortality. At the same time, the positive effect of ozone was observed in improvement of P/F ratio and Brixia score at day seven of ozone therapy. No side effects related to ozone therapy were observed in our study.

Key words: Ozone therapy, SARS-CoV-2, Pandemic, Autohemotherapy, COVID-19.

I. Introduction

The rapid and uncontrollable global spread of SARS-CoV-2 virus infection, as well as the huge number of deaths caused by COVID-19 disease, has necessitated the rapid search for effective drug remedies in various classes and with various mechanisms of action.

The COVID-19 pandemic has led to multidisciplinary approaches in medicine (public health, epidemiology, virology, immunology, pharmacology, infectious diseases, internal medicine, intensive care etc.) for the development of effective measures to fight infection.

In fact, initial treatments (antiviral, anti-inflammatory, anti-cytokine etc.) have been recommended either empirically, or based on in vivo results, or after the publication of the first articles, which reported positive results [1].

Various quasi-experimental protocols are being evaluated at the hospital level to modulate the excessive immune response, to suppress different proinflammatory cytokines, and thus to avoid the damage produced by the cytokine storm, because this phenomenon is responsible for the fatal outcome in infection by SARS-Cov-2.

Pre-Pandemic Experience using ozone therapy in various infections (microbial, fungi, viral, including SARS-COV1) has led to hypothesis that ozone therapy might be potentially beneficial in treatment of SARS-COV2 infection [2].

Since the First World War, blood ozonation has shown an effective bacterial effect. Furthermore, the diffusion of several studies regarding patient infected by Ebola and treated with O₃ therapy demonstrate its capacity to stimulate oxygen metabolism and to modulate the immune system [3].

Several countries including Cuba, Italy, Germany, Greece, Russia, and Spain have shown that ozone (O₃) is capable of modulating inflammation and pain, in addition to having demonstrated a bactericidal, fungicidal, virucidal, and antiparasitic effect, also incorporated ozone therapy in medical practice for many indications. The beneficial effects of ozone have been demonstrated in various studies. Ozone has been reported to be helpful in the treatment of different pathological disorders by inducing oxidative-antioxidative mechanisms. Besides, ozone provides oxygen substantially to tissues with poor oxygenation [4].

1.1 Ozone and Medicinal Properties

Ozone is a strong oxidizing agent (the third if compared to fluorine and persulfate) and a molecule with a high reactivity.

Ozone (O₃) is a gas composed of three atoms of oxygen, including a stable pair (O₂) and a third, unstable, atom, which gives ozone its beneficial effects on humans' health [5]. Several studies showed that ozone could improve blood circulation and oxy-

gen delivery to ischemic tissue. Thus, it may contribute to overcoming hypercoagulation, a frequently observed pathology in COVID-19 patients. Additionally, a hyperinflammatory response is a hallmark of severe SARS-CoV-2 infection and cytokine modulation is a key to avoid patients deterioration. Remarkably, ozone was able to modulate the release of anti-inflammatory cytokines, reduce the activity of pro-inflammatory cytokines and it has a direct antiviral effect suggesting its potential benefits in COVID-19 management [4–5].

Ozone has a dose/effect relationship and therefore is not considered a homeopathic medicine. On the contrary, ozone generators release concentrations from 1 to 70–100 µg/ml, although the therapeutic window is between 10 and 80 µg/ml.

Four properties are proposed for which ozone would be useful in the management of SARS-COV-2:

Antiviral effect: Rowen states that ozone is capable of directly inactivating many viruses (Norwalk virus, Hepatitis A virus, poliovirus and MS3 colofagus). The explanation for the “virucidal” effect is that ozone is capable of oxidizing the glycoprotein of its membrane, transforming it from the reduced form (R-S-H) to the oxidized form (R-S-S-R). The virus normally requires the reduced form to enter cells and infect them.

Mirazmi has observed that CMV (cytomegalovirus) loses infectivity if its “thiol” or sulfhydryl (R-S-H) group is oxidized (R-S-S-R), as Rowen observed. Coronaviruses, as well as Ebola virus, have regions rich in cysteine and tryptophan in their membrane S-protein (spike-S) [6].

If ozone by the peroxidation process damages the capsid, the reproductive cycle of the virus is altered, therein would be the therapeutic effect of ozone in the initial phase of early infection.

Immunomodulatory effect: Ozone, via second messengers (H₂O₂), is capable of stimulating cellular and humoral immunity, through the NFAT (nuclear factor activated T cells) signaling pathway and the AP-1 (activated protein-1) pathway [7].

These pathways are crucial transcription factors since they would induce the expression of genes to release inflammatory cytokines (IL-2, IL-6, IL-8, TNF-α, and IFN-γ) that will produce the inflammation that will recruit the neutrophils, lymphocytes, and macrophages, in order to carry out phagocytosis to limit infection at that level, killing local pathogens.

Antioxidant effect: Ozone at therapeutic doses modulates erythroid nuclear factor type 2 (Nrf2) and NF-κβ and induces the rebalancing of the antioxidant environment.

During acute inflammatory processes, to increase the magnitude of the response, NF-κβ promotes increased activity of mitochondrial NADPH oxidase, the main source of endogenous superoxide anion radical. It is now clear that there are strong links between the coordinated activity of gene activation by both transcription factors (NF-κβ and Nrf2) to solve inflammatory processes at the cellular and tissue level. An imbalance between the NF-κβ and Nrf2 routes is associated with a large number of diseases, as is the case of COVID-19 complications [8].

Fernández-Cuadros has stated that ozone is capable of blocking the NF-κβ pathway, decreasing proinflammatory cytokines IL-1, IL-6, TNF-α, and stimulating anti-inflammatory cytokines IL-4 and IL-10.

Furthermore, in a recent study, Fernández-Cuadros has observed that ozone is capable of modulating inflammation, decreasing inflammation markers such as CRP (C-reactive protein) and ESR (erythrocyte sedimentation rate). Due to these characteristics,

we believe that ozone could modulate inflammation and have a therapeutic role in the hyper inflammation phase, acting on the “cytokine storm” [9].

Stimulation of oxygen metabolism: Ozone could improve the circulation and perfusion of the lung and of all the organs in a state of hypoxia. Ozone improves the metabolism of oxygen. Ozonized erythrocytes show improved glycolysis with increased levels of ATP and 2,3-DPG (diphosphoglycerate), which can shift the HbO₂ dissociation curve to the right, increase arterial PO₂, and decrease venous PO₂ (Bhor effect), improving oxygen supply to ischemic tissues. Continuous applications of ozone stimulate the bone marrow and induce it to generate new “gifted erythrocytes” with an increase in the content of 2,3-DPG, as well as an elevation of glucose 6-phosphate dehydrogenase (G6PD); this may allow a profound modification of functional activities leading tissues and organs from a hypoxic to a normal oxygen state [10].

Ozone therapy stabilizes liver metabolism and plasma fibrinogen and prothrombin levels tend to normalize in infected patients, suggesting an improvement in the synthesis of liver proteins.

In this context, we reasonably believe that ozone has a place in the management of the present SARS-CoV-2 pandemic, so we will carry out a review on the subject and its therapeutic possibilities.

The objective of this clinical study is to analyze the therapeutic possibilities of ozone on SARS-Cov2 (COVID-19) infection according to evolutionary stage and perhaps propose its use as complementary therapy in the compassionate treatment of COVID-19, because it is the simplest, safest, and cheapest technique.

II. Materials and methods

II.1 Study design

This prospective randomized case-control clinical study was performed at the Institute of Emergency in Chisinau, Republic of Moldova. It was approved by a Research Ethics Committee of “Nicolae Testemitanu” State University of Medicine and Pharmacy of the Republic of Moldova. Each participant gave written informed consent for administration of any interventions collection of relevant clinical data and ascertainment of outcomes. The study consisted of all adults (aged ≥ 18 years) who were admitted to the ICU with a diagnosis of moderate COVID-19 pneumonia between 20th July 2020 and 5th February 2021. Eligibility criteria were: confirmed COVID-19 infection (diagnosed by nasopharyngeal swab performed on admission); pneumonia with baseline chest X-ray abnormalities with Brixia score 6-10 points and P/F ratio between 200 and 300.

The cohort of subjects consisted of one hundred patients eligible for enrolment.

Enrolled study participants were divided in two groups:

Control group (LC) – 50 patients, receive standard treatment according to the institutional protocol

Study group (LO)- 50 patients, receive standard treatment according to the institutional protocol+ ozonated-autohemotherapy (O₃-AHT).

II.2 Standard treatment care

Treatment for all COVID-19 pneumonia patients, in our institution, included options for providing enhanced respiratory support include using high-flow nasal canula (HFNC) oxygen, non-invasive ventilation (NIV), intubation and mechanical ventilation, corticosteroids (dexamethasone, methylprednisolone) and antibiotics (according to the antibiogram) at the discretion of the individual patient’s attending physician. Neither remdesivir nor tocilizumab were given to any patient. Enoxaparin 1 mg/kg SC q12h

was used as therapeutic anticoagulation dose. Decisions on endotracheal intubation, mechanical ventilation were made following clinical standards and at the discretion of the patient's attending physician.

II.3 Ozonated autohemotherapy (O3-AHT)

Ozonated blood was given once per day for 7 consecutive days. Ozonated autohemotherapy involved intravenous infusion of ozonated autologous whole blood. Initially, 150 mL of autologous whole blood was drawn from the patient's central vein with a 3.8% sodium citrate amount of 1:10. The blood was then enriched with 150 mL of gas mixture oxygen-ozone with an ozone concentration at 40 µg/mL obtained by *Hyper Medozon comfort*, an ozone generator with CE0123 certificate type I. The ozonized blood was then re-infused into the same vein over approximately 10–15 min.

Randomization was performed by a central computer system: G*Power 3

Analysis: A priori: Compute required sample size

Input: Effect size $w = 0.3$

α err prob = 0.05 Power (1- β err prob) = 0.8

Df = 1

Output: Non centrality parameter $\lambda = 7.9200000$

Critical $\chi^2 = 3.8414588$

Total sample size = 88

Actual power = 0.8035275

III. Results

A total of 869 patients with severe or critical form of COVID-19 were admitted in ICU, and 100 eligible patients were enrolled (Figure 1). In the studied groups (LC vs LO) the mean age presented a value of 61 (median, IQR = 17) years compared to 60 years (median, IQR = 13), different detected being insignificant (Mann-Whitney test $U = 1012$, $p = 0.101$). Comparing the study groups according to the biological criteria, they did

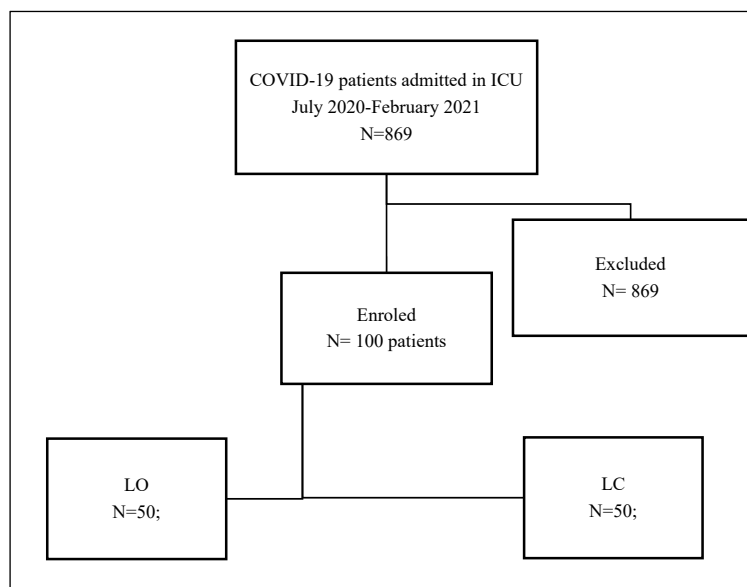


Fig. 1. Study flow chart. ICU: Intensive Care Unit; LO: Study group; LC: Control group.

not detect different significant statistics (test $X^2 = 0.161$, $df = 1$, $p = 0.548$). LC included 25 men, which constitutes 50% (95% CI 36.5, 63.5) of the total number of subjects, LO having 22 men (44%, 95% CI 30.9, 57.8). At the same time, the analysis of the relative frequencies of the blood group after ABO showed a statistically significant difference for group O (I), which predominated in LO (40% (CI95% 27.3, 53.8) vs 20% (CI95% 10.8, 32.6), $p < 0.05$) if group AB (IV), which predominated in LC (14% (CI95% 6.5, 25.) vs 0%, $p < 0.05$). At the same time LC and LO were identical after Rh- res factor.

The analysis of concomitant pathologies shows predominance in LC compared to LO of patients with hypertension (72% (CI 95% 58.6, 83) compared to 50% (CI95% 36.5, 63.5), test $X^2 = 4.203$, $df = 1$, $p = 0.04$). Type II diabetes showed similar trends without statistical significance (44% (CI95% 30.9, 57.8) versus 28% (CI95% 17, 41.4), test $X^2 = 2.172$, $df = 1$, $p = 0.145$). Patients with atrial fibrillation were assigned in ratios 6% (CI95% 1.7, 15.2) in LC to 2% (CI95% 0.2, 9.0), the differences being insignificant (test $X^2 = 0.260$, $df = 1$, $p = 0.610$). The same trend was found for obese patients, LC compared to LO having 40% (CI95% 27.3, 53.8) vs 26% (CI95% 15.4, 39.3, test $\chi^2 = 1.628$, $df = 1$, $p = 0.202$). In contrast, the relative frequencies of COPD predominated without statistical significance in LO. Thus, COPD was not detected in LC, LO having 5 patients (10%, CI95% 3.9, 20.5) with the given pathology (test $\chi^2 = 3.368$, $df = 1$, $p = 0.066$). The frequencies of asthma in the studied groups were identical, 1 case from each group (Table 1).

Table 2 presents result of primary and secondary outcomes.

The primary outcome was analyzed and the absolute and relative values in LC were higher. The mortality in LC group versus LO was 34% (CI95% 22.1, 47.7) and 26% (CI 95% 15.4, 39.3), respectively. However, no statistical significance between LC and LO was established (X^2 test = 0.429, $df = 1$, $p = 0.513$, OR = 0.682 (CI95% 0.288, 1.614)). P/F ratio on day 7 in LO group was higher in study group 287 (IQR 150) vs 210 (180.75) with statistical significance ($p = 0.007$). Brixia score at day 7th of ozone therapy was lower in study group 8 (IQR-5) vs 9 (IQR - 7) ($p = 0.037$).

The secondary outcome as non-invasive ventilation (NIV), mechanical ventilation (MV) duration and ICU, days did not show any significance among the examined groups.

The NIV duration in LC was practice identical in comparison to LO (Median = 3, IQR = 4 versus Median = 3, IQR = 7, Mann-Withney U test = 1296.5, $p = 0.746$).

Table 1

Patients' baseline demographic and clinical characteristics. LO: Study group; LC: Control group

Variable	LC (n=50)	LO (n=50)	p Value
Age, years median (IQR)	61 (17)	60 (13)	0.101
Male, n (%)	25 (50%)	22 (44%)	0.548
Hypertension, n (%)	36 (72%)	25 (50%)	0.04
Diabetes Mellitus, n (%)	22 (44%)	14 (28%)	0.145
Obesity, n (%)	20 (40%)	12 (24%)	0.202
Atrial fibrillation, n (%)	3 (6%)	1 (2%)	0.610
COPD, n (%)	-	5 (10%)	0.066
Blood group (ABO) – O(I), n (%)	10 (20%)	20 (40%)	0.05
Blood group (ABO) – AB(IV), n (%)	7 (14%)	-	0.05

Table 2

Primary and secondary outcomes. LO: Study group; LC: Control group; IQR: interquartile

Variable	LC	LO	p Value
Primary outcome			
Mortality, n (%)	17 (34%)	13 (26%)	0.513
Secondary outcome			
NIV duration, days median (IQR)	3 (4)	3 (7)	0.746
MV duration, days median (IQR)	0 (5)	0 (0)	0.118
ICU length of stay, days median (IQR)	7(6)	7 (9)	0.761
Hospital length of stay, days median (IQR)	13 (10.5)	17 (9)	0.215
P/F ratio on 1 st day of therapy, days median (IQR)	227 (58)	247 (56)	0.101
P/F ratio on 7th day of therapy, days median (IQR)	210 (180.75)	287 (150)	0.007
Brixia score on 1 st day of therapy, days median (IQR)	8 (2)	9 (4)	0.960
Brixia score on 7th day of therapy, days median (IQR)	9 (7)	8 (5)	0.037

The MV duration in LC was practice identical in comparison to LO (Median = 0, IQR = 5 versus Median = 0, IQR = 0, Mann-Whitney U test = 1064.5, p = 0.118).

The effect of ozone therapy was estimated in multivariate analysis.

IV. Discussion

Currently there are no studies that demonstrate the influence of ozone therapy on the mortality rate, length of hospital stay, or both, in patients with Covid-19. However, some authors have hypothesized that there may be a relationship between intravenous ozone therapy and clinical outcomes [11–13; 15]. In this study was observed increased mortality rate in control group, but without statistical significance. Supposable, that higher number of patients is necessary to confirm this hypothesis.

Since the beginning of pandemic a series of studies researching ozone therapy have been performed. A range of aspects were studied. In a single center case series study on 50 male more than 60 years hospitalized COVID-19 subjects suffering from acute respiratory disease syndrome (ARDS) performed by Franzini M. [12] has showed the recovery of normal functional pulmonary parameters in less than 10 days (median 13.45 ± 2.33 days), respect to the expected.

In a prospective case-control study in Spain performed by Hernández A. [11] on 18 patients with COVID-19 infection with severe pneumonia admitted to hospital ozonated autohemotherapy was associated with a significantly lower time to clinical improvement (median [IQR]), 7 days [6–10] vs 28 days [8–31], p = 0.04), the groups being small as number and unbalanced as age. Our data suggest that the ICU and hospital stay don't differ statistically in patients with ozone therapy and who did not received it.

In a case-control study in Italy enrolling 60 subjects with modest to moderate respiratory insufficiency mortality was observed in only two cases in the control group. The low rate of mortality was attributed to the patients' profiles enrolled in study [13].

In a randomized trial conducted in four different Italian centers by Cormor on 92 patients (the largest sample so far studied) the mortality rate was the same in both groups of patients with mild to moderate COVID-19 pneumonia (4.7% in SOC and 4.2% in O3-ATH) [14].

In SEOT randomized control trial on 60 patients 2 fatalities were reported in the ST group due to progression of COVID-19. Comparison between the two groups on Fisher Exact Test indicated a statistically significant ($P < 0.05$) change. However results seem dubious because of only 2 reported lethal cases in control group versus no lethal cases in the ozone group (Fisher Exact Test being non significant) [15].

Beside primary outcomes, other parameters were studied by various researches. Among them influence of ozone therapy on oxygenation was investigated. Fanzini suggests a possible O_2 saturation improvement due to O_2-O_3 treatment. The difference within study group before and after ozone therapy was estimated as 13% ($p < 0.001$), PaO_2/FiO_2 ratio increased by 4.5 units ($p = 0.00456$), the Hb and arterial pressure level being with no modification [12]. However the weakness of these results is represented by the fact that this was a case series and there was no control group. In presented research were registered increased and improved values the P/F ratio and slightly higher values of Brixia score after seven days of ozone therapy.

In CORMOR study there was not a significant change in the baseline PaO_2/FiO_2 ratio and this parameter had better time-course in the ozone therapy group. Some aspects of inflammatory response were described such as reduction of CRP and IL-6 (about 48.15% (covariance = 9576.177, $p = 0.0167$), and 86.17% (covariance = 9113.337, $p = 0.0275$), respectively), reductions for bacterial-mediated inflammation markers (pro-calcitonin, PCT) and fasting glucose, despite the hypoglycemic effect of O_2-O_3 treatment was non-significant ($p > 0.05$), but insignificant effect on the increase in leukocytes. CORMOR study reports a significant difference in terms of low white blood cells count and elevated C reactive protein as opposed to the control group, but these differences were not observed on the one week from end of blood ozonation, on the end of treatment [14].

The impression is that there is generally a paucity of articles studying influence of Ozone in Covid-19 patients. Moreover, analyzing existing studies a series of gaps are noted. One of the gaps is the fact that studies till now are not covering effects of ozone therapy on ICU patients.

V. Conclusions

In this study, was demonstrated that application of ozone therapy, like a complimentary support to COVID-19 hospitalized patients does not influence the mortality. At the same time, the positive effect of ozone was observed in improvement of P/F ratio and Brixia score at day seven of ozone therapy. No side effects related to ozone therapy were observed in our study.

VI. Limitation

It is a single center, small study population.

VII. Acknowledgments

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VIII. Conflict of interest

The authors declare no conflict of interest.

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