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Desperate Times for Pandemic Lead to... Ozone?

— Case study in three patients with severe COVID-19 pneumonia

by Kate Kneisel, Contributing Writer, MedPage Today
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Three patients present to a hospital emergency department in Ibiza, Spain, with severe COVID-19 pneumonia and respiratory failure and are given an unproven -- and possibly dangerous -- treatment: oxygen-ozone (O_2-O_3) therapy -- also called ozonated autohemotherapy, which has been used to treat gout and involves intravenous infusion of ozonated autologous whole blood.

The FDA has called ozone "a toxic gas with no known useful medical application." Furthermore, in April 2020, a federal court entered a permanent injunction halting a purported "ozone therapy" center in Dallas from offering unproven treatments for COVID-19, after the company claimed that the treatments were able to "eradicate" the virus and were 95% effective in preventing the illness even for individuals who had tested positive.

As described in this case report, published on Aug. 17, 2020, of three patients in Spain, the clinicians drew 200 mL of autologous whole blood from the antecubital vein into a standard plastic disposable blood collection bag (certified $SANO_3$ bag) with 35 mL of anticoagulant citrate dextrose solution. The team enriched the blood with 200 mL of gas mixture O_2-O_3 with an ozone concentration of 40 µg/mL obtained using an ozone generator with CE0120 certificate type IIb. This was followed by reinfusion of the ozonized blood using the same vein over approximately 10 minutes.

Patient 1

Patient 1, a 49-year-old man, body mass index (BMI) of 31, reported having 1 week of ongoing abdominal pain, and that over the course of the previous day he had increasing shortness of breath. Examination finds a soft abdomen with no distension.

Upon auscultation of his chest, clinicians noted bilateral crackles with reduced air entry and ordered a computed tomography (CT) scan of the chest and abdomen, which identified lung infiltrates in both lungs, compatible with COVID-19 pneumonia. Laboratory tests show elevated levels of:

- Ferritin (1,609 ng/mL)
- D-dimer (1,900 ng/dL)
- C-reactive protein (CRP, 17.3 mg/dL)
- Lactate dehydrogenase (LDH, 536 IU/L)

Clinicians took a nasopharyngeal swab; real-time polymerase chain reaction (RT-PCR) analysis identified the sample as positive for viral RNA, and the man is admitted to the intensive care unit (ICU). Over the following 24 hours, his condition improves and he is transferred to the general ward.

However, during the following day, the patient's oxygen levels declined, followed by respiratory distress, with a PaO2/FiO2 [partial pressure of arterial oxygen/percentage of inspired oxygen] ratio of 235. Clinicians put the patient on a non-rebreather face mask with oxygen on FiO2 of 0.8, and noninvasive ventilation (NIV) is not required. An x-ray revealed diffuse bilateral infiltrates.

For the next 3 days, the patient received two sessions of ozone autohemotherapy daily q 12 hours. He had a rapid clinical response, as evidenced by a marked improvement in respiratory rate and an increased PaO2/FiO2 ratio, with decreased FiO2 to 0.31% (3 L) after 1 day. After 2 sessions of ozone therapy, the patient's ferritin levels dropped from over 2,000 to 246 ng/mL, and his D-dimer levels dropped from 1,900 to 323 ng/mL.

On day 4, the patient was discharged home.

Chest x-ray before (A) and after (B) two sessions of oxygen-ozone therapy.

Ozone can induce the release and modulation of which of the following cytokines?

- [ ] Interleukin-2
- [ ] Interferon-gamma
- [ ] Tumor necrosis factor
- [ ] All of the above

Patient 2

The second patient, a 61-year-old man, BMI of 29, presented a week after developing a persistent fever of over 39°C. He reported having long-standing hypertension and becoming progressively short of breath over the previous 2 days. Chest auscultation showed crackles with reduced air entry over the right hemithorax. CT of the chest–abdomen revealed right upper infiltrates suggestive of COVID-19 pneumonia. Baseline PaO2/FiO2 was 253.

Laboratory tests showed high levels of:

- Ferritin (2,200 ng/mL)
- D-dimer (3,660 ng/mL)
- CRP (10 mg/dL)

- LDH (816 IU/L)

The patient remained in the general ward, where he received oxygen at an FiO2 of 0.6 via face mask, and he did not require NIV.

For the following 2 days, he received two sessions of ozone autohemotherapy over a period of 24 hours. On day 3, clinicians noted a decline in the FiO2 of 0.31% (3 L) with improved PaO2 to 90 mmHg, and decreased levels of laboratory markers.

The patient was discharged home on day 3 after a total of four sessions of O_2-O_3 therapy. Post-discharge, clinicians reported that the patient's LDH levels dropped from 816 U/L at baseline to 469 U/L by day 6 after the start of ozone therapy. Likewise, his CRP levels began falling progressively after initiation of ozone therapy, from 10 mg/dL at the time of presentation to approximately 4 mg/dL on day 3 and about 0 mg/dL on day 21.

What is the maximum ozone output of indoor medical devices permitted by the FDA in parts per million (ppm)?

0.03 ppm

0.05 ppm

0.07 ppm

0.09 ppm

Patient 3

The third patient, a 64-year-old woman with a BMI of 20, presented with progressive shortness of breath over 3 days. Clinicians diagnosed her with COVID pneumonia, and took a nasopharyngeal swab sample. Laboratory tests showed high levels of:

- Ferritin (656 ng/mL)
- D-dimer (657 ng/dL)

- CRP (5 mg/dL)
- LDH (452 IU/L)

RT-PCR analysis of the swab was positive for viral RNA; baseline PaO2/FiO2 is 243. The patient is admitted to the general ward, where she received oxygen at an FiO2 of 0.8 via face mask; NIV is not required. Clinicians immediately initiated O_2-O_3 therapy.

Treatment was followed by rapid recovery as demonstrated by the patient's clinical and laboratory profiles, which were similar to those of Patients 1 and 2. Her D-Dimer levels dropped from 657 to approximately 130 ng/mL 1 day after ozone therapy and remained at 100 -200 ng/mL for the next 4 days.

CRP levels fell to 1 mg/dL on day 2 and continued to decline for the patient's remaining time in the hospital. She received six sessions of O_2-O_3 therapy in total, and was discharged to home on day 4 after ozone therapy.

Discussion

Clinicians reporting these three cases noted that in all the patients, four to six sessions of ozonated autohemotherapy was associated with early discharge from the hospital without the need for invasive ventilation.

The authors noted that there is no effective treatment for COVID-19 pneumonia and only limited understanding of the pathogenesis of the virus, resulting in a growing use of novel methods. Ozone is known to have antipathogenic activity and can induce the release and modulation of interferons and related cytokines, such as interleukin (IL)-2, interferon-gamma, tumor necrosis factor, and colony-stimulating factors; ozone can also modulate and stimulate phagocytic function, which may explain its potential benefits in treatment of COVID-19 infection, the case authors speculated.

They explained that medical ozone generators produce 1-5% ozone gas in 95-99% oxygen from pure oxygen, and that therapeutic applications generally use concentrations of 10-70 µg/mL. As described, the process of "ozonated autohemotherapy" involves systemic

delivery of ozone therapy by adding it to a sample of a patient's blood and then reinfusing it.

When blood is exposed to this gas mixture , oxygen equilibrates with the extracellular and intra-erythrocytic water before becoming bound to hemoglobin until it is fully oxygenated, the authors explained. They added that since ozone is approximately 10 times more soluble than oxygen, it reacts immediately with any soluble compounds and biomolecules such as ascorbic acid, urate, free cysteine, glutathione molecules, and albumin thiol groups, and then disappears.

The theory, the authors said, is that the reaction process – i.e., reactive oxygen species and lipid ozonation products – generates compounds that act as "ozone messengers," thus theoretically providing ozone's presumed biological effects. Ozone can deliver sufficient energy and oxygen to the tissues through several mechanisms: (1) by activating the pentose phosphate pathway; (2) by elevating 2,3-diphosphoglyceric acid content in erythrocytes; and (3) by stimulating erythrocyte oxygen metabolism.

Angiotensin-converting enzyme 2 is an entry receptor for COVID-19 that can be blocked by control of the nuclear factor erythroid 2-related factor 2 (Nrf2), which controls the activity of this receptor, the case authors continued. They suggested that ozone's rapid activation of Nrf2 activation may help block endogenous COVID-19 reduplication by preventing contact with this receptor. In addition, the authors said, ozone therapy could theoretically decrease the hypercoagulation phenomena associated with COVID-19 by improving the rheology and capillary action of blood, which has been reported to be beneficial in ischemic vascular diseases.

Comments 11

I am biased. I have had a positive experience with O3. In an infection (viral) that I couldn't shake, a good Doctor said, "Ozone?". I said "Let's do it". Within hours I began to feel better and I cleared the bug in 72 hours.

The FDA is wrong in its ozone assessment.

Ralph Dratman

August 27, 2020

Like any proposed therapeutic regimen, this technique requires multiple detailed studies to determine safety and efficacy.

Koray Tascilar

August 27, 2020

Wow, the degree at which quackery has infiltrated medicine is astounding. I put it wrong, I think more astounding is our failure as physicians to allow this infiltration. The best defining characteristic of quackery is that it never fails and is always a panacea with all sorts of beneficial effects for all sorts of ailments north and south.

Robert Silvetz, MD

August 27, 2020

@Koray Tascilar. Far too critical. There is more in and out of medicine than there is dreamt of in your philosophy (with apologies to the Bard).

I have walked outside orthodoxy now for better than 30 years, quite rigorously looking at both accepted and non-accepted therapy. Interestingly, the quacks, as you call them, get results. One thing those of us who have walked outside orthodoxy notice is that the quacks are never tested under the conditions which the "quacks" articulated. A peculiar fact that is almost always true. We just saw this with HCQ. Not one of

Also unrelated to the novel coronavirus, a 2018 report published by the Spanish Association of Medical Professionals in Ozone Therapy noted "growing interest" in the technique among medical professionals, as assessed by MEDLINE/PubMed searches showing 235 clinical studies; the association noted that the European Medicines Agency includes ozone as an authorized active substance and has active projects in research.

Conclusions

The case authors concluded by stating that while O_2-O_3 therapy appeared to lead to improvement in these three COVID-19 patients with severe respiratory failure, the method remains unproven, and the only way to know whether it is indeed effective is to conduct large controlled clinical trials to study the efficacy and safety compared with standard supportive care in terms of the need for invasive ventilation and length of stay in the hospital and ICU.

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Disclosures

The case report authors noted no conflicts of interest.

Primary Source

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