

Updates on the Use of Ozone Therapy in Patients with COVID-19. A Review

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Abstract

To date, there are no specific antiviral treatment strategies for COVID-19 patients. Empiric approaches used for other viral infections wasn't effective against SARS-CoV-2. Thus, some urgent therapeutic alternatives are still required. Ozone therapy could be favorable due to its effects. Therefore, authors conducted a comprehensive review to reassess the reported adjuvant clinical potency and the last medical approaches towards patients with SARS-CoV-2 virus or COVID-19. Relevant articles were searched in PubMed, Hinari and SpringerLink, National Center of Biotechnology Information, and Medline using keywords "COVID-19", "SARS-CoV-2", "ozone therapy", "mechanisms of ozone", and "biological effects of ozone", as well as their combinations. A total of 475 publications found were compared to exclude duplicates. The collection was reviewed and articles were filtered by title and abstract content. The remaining articles were assessed in full to exclude case-control studies or articles without relevant conclusions. Finally, 49 relevant sources were selected as representative. Ozone therapy has shown various beneficial properties: antiviral, immunomodulatory, antioxidant, anti-inflammatory, and cytoprotective effects, that can be useful in managing tissue damage occurring in many inflammatory illnesses, including viral infections like SARS-CoV-2. It can enhance the respiratory parameters, blood gas indicators, overall health condition, leading to a faster patient recovery.



Despite encouraging preliminary data from ongoing clinical trials, as well as expert opinion, there is still not enough evidence to confirm that it is a viable treatment for patients with COVID-19.

Keywords: Covid-19, ozone therapy, ozone action mechanisms

References

- 1. Malik, P., et al.: Biomarkers and outcomes of COVID-19 hospitalisations: systematic review and meta-analysis. BMJ Evidence-based Med. **26**, 107–108 (2021). https://doi.org/10.1136/BMJEBM-2020-111536
- 2. Coronavirus disease (COVID-19), https://www.who.int/emergencies/diseases/novel-coronavirus-2019
- 3. Fernández-Cuadros, M.E., María, Albaladejo-Florín, J., Peña-Lora, D., Álava-Rabasa, S., Susana Pérez-Moro, O.: Ozone (O3) and SARS-CoV-2: Physiological Bases and Their Therapeutic Possibilities According to COVID-19 Evolutionary Stage. https://doi.org/10.1007/s42399-020-00328-7/Published
- 4. Sahin, M., Eryilmaz, F., Keser , Sahin, H: Ozone therapy may be an option for COVID-19 patients. 2470–2472 (2021). https://doi.org/10.26355/eurrev_202103_25407
- 5. Hernández, A., Viñals, M., Isidoro, T., Vilás, F.: Potential Role of Oxygen-Ozone Therapy in Treatment of COVID-19 Pneumonia. Am. J. Case Rep. **21**, 1–6 (2020). https://doi.org/10.12659/AJCR.925849
- 6. Yilmaz, N., Eren, E., Oz, C.: COVID-19 and Ozone. Cyprus J. Med. Sci. **5**, 365–372 (2021). https://doi.org/10.5152/cjms.2020.2658
- 7. Ricevuti, G., Franzini, M., Valdenassi, L.: Oxygen-ozone immunoceutical therapy in COVID-19 outbreak: facts and figures. Ozone Ther. **5**, (2020). https://doi.org/10.4081/OZONE.2020.9014
- 8. Heimfarth, L., Serafini, M.R., Martins-Filho, P.R., Quintans, J. de S.S., Quintans-Júnior, L.J.: Drug repurposing and cytokine management in response to COVID-19: A review. Int. Immunopharmacol. **88**, (2020). https://doi.org/10.1016/J.INTIMP.2020.106947
- 9. Da, D., Campos, S., Morais, J.P., Tim, C.R., Gomes, J.C., Assis, L.: Implications for the use of ozone (O3) in the adjuvant treatment of COVID-19. Res. Soc. Dev. **9**, e579997508–e579997508 (2020). https://doi.org/10.33448/RSD-V9I9.7508



- 10. Cattel, F., et al.: Ozone therapy in COVID-19: A narrative review. Virus Res. **291**, (2021). https://doi.org/10.1016/J.VIRUSRES.2020.198207
- 11. De Farias, J.B.F., De Farias, A.P.F., De Souza, A.G.: Ozone as a complement therapy in the treatment of COVID-19. Rev. Bras. Fisiol. do Exerc. cio. **19**, 5–8 (2020). https://doi.org/10.33233/RBFE.V19I2.4116
- 12. Ogut, E., Armagan, K.: Evaluation of the potential impact of medical ozone therapy on covid-19: a review study. Ozone Sci. Eng. (2022). https://doi.org/10.1080/01919512.2022.2065242
- 13. Promoter of the study: NUOVA F.I.O. (Italian Oxygen-Ozone Federation), Marini, S., et al.: Oxygen-ozone therapy as adjuvant in the current emergency in SARS-COV-2 infection: clinical study. J. Biol. Regul. Homeost. Agents. 34, (2020). https://doi.org/10.23812/20-250-E-56
- 14. Martínez-Sánchez, G.: Ozone Therapy for Prevention and Treatment of COVID-19. J. Explor. Res. Pharmacol. 000, 000–000 (2022). https://doi.org/10.14218/JERP.2022.00015
- 15. Radvar, S., et al.: Using ozone therapy as an option for treatment of COVID-19 patients: a scoping review. Adv. Exp. Med. Biol. **1327**, 151–160 (2021). https://doi.org/10.1007/978-3-030-71697-4_12
- 16. Alberto Hernández, A., Vilás, F., Papadakos, P.J., Bergese, S.D., Vives, M.: Title: Ozone therapy for patients with COVID-19 pneumonia: preliminary report of a prospective casecontrol study. https://doi.org/10.1101/2020.06.03.20117994
- 17. Martínez-Sánchez, G., Schwartz, A., Di Donna, V.: Potential cytoprotective activity of ozone therapy in SARS-CoV-2/COVID-19. Antioxidants. **9**, (2020). https://doi.org/10.3390/antiox9050389
- 18. Fernandez-Cuadros, M.E., Perez-Moro, O.S., Albaladejo-Florin, M.J., Entrambasaguas-Estepa, B., Alava-Rabasa, S.: Mid-Term Effectiveness of Ozone (O2-O3) Compared to Platelet-Rich Plasma (PRP) in the Management of Knee Osteoarthritis: A Randomized Parallel Controlled Trial. Middle East J. Rehabil. Heal. In: Press, 1–8 (2019). https://doi.org/10.5812/mejrh.74140
- 19. Barbosa, R.B., et al.: Ozone therapy as a treatment option against COVID-19: a literature review. Res. Soc.Dev. **10**, e469101321228–e469101321228 (2021). https://doi.org/10.33448/RSD-V10I13.21228
- 20. Fernández-Cuadros, M.E., et al.: Compassionate use of rectal ozone (O3) in severe COVID-19 Pneumonia: a case-control study. SN Compr. Clin.Med. **3**, 1185–1199 (2021). https://doi.org/10.1007/S42399-021-00849-9



- 21. Wang, Y., et al.: Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet (London, England). **395**, 1569–1578 (2020). https://doi.org/10.1016/S0140-6736(20)31022-9
- 22. Izadi, M., et al.: Ozone therapy for the treatment of COVID-19 pneumonia: a scoping review. Int. Immunopharmacol. **92**, 1567–5769 (2021). https://doi.org/10.1016/j.intimp.2020.107307
- 23. Rowen, R.J., Robins, H.: A Plausible "Penny" Costing Effective Treatment for Corona Virus Ozone Therapy. J Infect Dis Epidemiol. **2020**, 113 (2020). https://doi.org/10.23937/2474-3658/1510113
- 24. Sharma, A., et al.: A pilot study for treatment of COVID-19 patients in moderate stage using intravenous administration of ozonized saline as an adjuvant treatment-registered clinical trial. Int. Immunopharmacol. **96**, (2021). https://doi.org/10.1016/J.INTIMP.2021.107743
- 25. Cenci, A., Macchia, I., La Sorsa, V., Sbarigia, C., Di Donna, V., Pietraforte, D.: Mechanisms of Action of Ozone Therapy in Emerging Viral Diseases: Immunomodulatory Effects and Therapeutic Advantages With Reference to SARS-CoV-2. Front. Microbiol. **13**, (2022). https://doi.org/10.3389/FMICB.2022.871645/PDF
- 26. Cuadros, M.E.F., Florín, M.J.A., Rabasa, S.Á., Lora, D.P.,Moro, O.S.P.: Ozone and COVID-19: physiological bases and their therapeutic possibilities according to the evolutionary stage in SARS-CoV-2 infection. Rev. la Soc. Esp. del Dolor. **28**, 27–36 (2021). https://doi.org/10.20986/RESED.2021.3810/2020
- 27. Yaneva, G., Dimitrova, T., Ivanov, D., Ivanova, D., Ingilizova, G., Slavov, S.: MODERN APPLICATIONS OF OZONE FOR COVID-19 DISINFECTION AND TREATMENT. J. IMAB Annu. Proceeding (Scientific Pap. 28, 4284–4288 (2022). https://doi.org/10.5272/JIMAB.2022281.4284
- 28. Manjunath, S.N., Sakar, M., Katapadi, M., Geetha Balakrishna, R.: Recent case studies on the use of ozone to combat coronavirus: Problems and perspectives. Environ. Technol. Innov. **21**, (2021). https://doi.org/10.1016/J.ETI.2020.101313
- 29. Falcón, B.A., Fernández, J.L.C., Cepero, S.M., Yoshimoto, C.V.: Ozone therapy and its application in relation to the pathophysiology of COVID 19 disease. Panor. Cuba y Salud. **15**, 104–107 (2020)
- 30. Yousefi, B., Banihashemian, S.Z., Feyzabadi, Z.K., Hasanpour, S., Kokhaei, P.: Potential therapeutic effect of oxygen-ozone in controlling of COVID-19 disease, pp. 33–40 (2022). https://doi.org/10.4103/2045-9912.325989



- 31. León Fernández, O.S., et al.: Medical ozone: the pharmacological mechanisms accounting for its effectiveness against COVID-19/SARS-COV-2. J.Med.-Clin. Res. Rev. ISSN **5**(1–10), 2639–2944 (2021)
- 32. Chirumbolo, S., et al.: Insights on the mechanisms of action of ozone in the medical therapy againstCOVID-19. Int. Immunopharmacol. **96**, 107777 (2021).

https://doi.org/10.1016/J.INTIMP.2021.107777

- 33. Schwartz, Martínez-Sánchez: Potential use of ozone in SARS-CoV-2 / COVID-19. Int. Sci. Comm. Ozone Ther. (2020)
- 34. Chirumbolo, S., et al.: Insights on the mechanisms of action of ozone in the medical therapy against COVID-19. Int. Immunopharmacol. **96**, (2021). https://doi.org/10.1016/J.INTIMP.2021.107777
- 35. Zheng, Z., Dong, M., Hu, K.: A preliminary evaluation on the efficacy of ozone therapy in the treatment of COVID-19. J. Med. Virol. **92**, 2348–2350 (2020). https://doi.org/10.1002/JMV.26040
- 36. Tricarico, G., Travagli, V.: The relationship between ozone and human blood in the course of a well-controlled, mild, and transitory oxidative eustress. Antioxidants. **10**, 1946 (2021).

https://doi.org/10.3390/antiox10121946

- 37. Morrison, C., et al.: Critical review and research needs of ozone applications related to virus inactivation: potential implications for SARS-CoV-2. Ozone Sci. Eng. **43**, 2–20 (2021). https://doi.org/10.1080/01919512.2020.1839739
- 38. Fernández-cuadros, M., Albaladejo-florín, M.J., Pérez-moro, O., Rodríguez-de-cía, J.: Multicentric Study on the Effect of Rectal Ozone on COVID-19: the Spanish and Slovakian Experience. (2022). https://doi.org/10.20944/preprints202203.0272.v1
- 39. Fernández-Cuadros, M.E., et al.: Effect of rectal ozone (O3) in SevereCOVID-19 Pneumonia: preliminary results. SN Compr. Clin.Med. **2**, 1328–1336 (2020). https://doi.org/10.1007/s42399-020-00374-1
- 40. Tascini, C., et al.:Monte, Amato: Blood ozonization in patientswith mild to moderateCOVID-19 pneumonia: a single centre experience. Intern. Emerg. Med. **16**, 669–675 (2021). https://doi.org/10.1007/s11739-020-02542-6
- 41. Franzini, M., et al.: Oxygen-ozone (O2-O3) immunoceutical therapy for patientswith COVID-19. Preliminary evidence reported. Int. Immunopharmacol. **88**, (2020). https://doi.org/10.1016/J.INTIMP.2020.106879



- 42. Çolak, S., et al.: Effectiveness of ozone therapy in addition to conventional treatment on mortality in patients with COVID-19. Int. J. Clin. Pract. **75**, (2021). https://doi.org/10.1111/ijcp.14321
- 43. Peña-Lora, D.Y., Albaladejo-Florín, M.J., Fernández-Cuadros, M.E.: Usefulness of rectal ozonetherapy in a geriatric patient with severe COVID-19 pneumonia. Rev. Esp. Geriatr. Gerontol. **55**, 362–364 (2020). https://doi.org/10.1016/J.REGG.2020.07.005
- 44. Shah,M., et al.: Safety and efficacy of ozone therapy inmild to moderate COVID-19 patients: A phase 1/11 randomized control trial (SEOT study). Int. Immunopharmacol. **91**, (2021). https://doi.org/10.1016/J.INTIMP.2020.107301
- 45. Sozio, E., et al.: CORonavirus-19 mild to moderate pneumonia management with blood ozonization in patients with respiratory failure (CORMOR) multicentric prospective randomized clinical trial. Int. Immunopharmacol. **98**, (2021). https://doi.org/10.1016/J.INTIMP.2021.107874
- 46. Schwartz, A., Martínez-Sánchez, G., de Lucía, A.M., Viana, S.M., Constanta, A.M.: Complementary application of the ozonized saline solution inmild and severe patientswith pneumonia COVID-19: A non-randomized pilot study. J. Pharm. Pharmacogn. Res. **9**, 126–146 (2021). https://doi.org/10.56499/JPPRES20.971_9.2.126
- 47. Setyo Budi, D., et al.: Ozone as an adjuvant therapy for COVID-19: A systematic review and meta-analysis. Int. Immunopharmacol. **110**, (2022). https://doi.org/10.1016/J.INTIMP.2022.109014
- 48. Robert Jay, R., Howard, R.: A plausible penny costing effective treatment for corona virus -ozone therapy. J. Infect. Dis. Epidemiol. **6**, (2020). https://doi.org/10.23937/2474-3658/1510113
- 49. Chirumbolo, S., et l.: The Mito-Hormetic mechanisms of ozone in the clearance of SARSCoV2 and in the COVID-19 Therapy. Biomed. **10**, (2022). https://doi.org/10.3390/BIOMEDICINES10092258