

Editorial – A practical assessment to prevent serious complications in the use of a gaseous mixture of oxygen-ozone injected by needle-mediated infiltration

S. CHIRUMBOLO, V. SIMONETTI, L. VALDENASSI, S. PANDOLFI,
F. VAIANO, M. FRANZINI

Oxygen-Ozone Therapy Scientific Society (SIOOT), Gorle, Italy; SIOOT, High School in Oxygen Ozone Therapy, University of Pavia, Italy; SIOOT INTERNATIONAL, Communian Clinic, Gorle Bergamo, Italy

Does ozone cause encephalopathy? In this paper, we would like to amend this somehow misleading consideration. What is true is that using ozone as an immune-pharmaceutical active substance may lead to severe adverse effects, if the physician's expertise is not fully trained. In this respect, some authors recently outlined the dangerousness of using ozone in medical practice. In their opinion, ozone may be toxic for the central nervous system by inducing encephalopathy¹.

Toxicity of ozone is usually associated with the use of empirical or not standardized protocols or, much rarely, because of poorly trained professionals. Some colleagues prefer to adopt empirical and not standardized methods in using medical ozone, rarely taking into consideration recommendations forwarded by leading authorities, such as the Italian Head Health Institute (Istituto Superiore di Sanità) or (ISS), in the Italian language. Actually, the local Scientific Societies engaged in the research and application of the oxygen-ozone therapy for neurology, orthopedics and neurosurgery, allows physicians to routinely apply these recommendations in their medical practice². The Italian Society of Oxygen Ozone Therapy (SIOOT) currently rules these guidelines, allowing physicians to earn important outcomes in the use of oxygen-ozone therapy in fatigue, both in post-COVID syndrome and cancer-related fatigue³⁻⁶.

Oxygen-ozone administration *via* needle is regulated by compulsory rules². Some authors¹ arranged a study fundamentally on less than 12 case reports; yet, they poorly detailed either how ozone therapy was performed or which therapeutic protocol using ozone was adopted in the eight case reports they addressed further¹. Accounting on few cases may generate bias in the thorough comprehension of how ozone actually works in a clinical setting, generating equivocal interpretations about the ozone toxicology. A deeper investigation¹ on several case reports, some of which reported elsewhere, allowed us to assess the existence of bias in using ozone for therapy in the neuropathic pain. This circumstance is usually due to the compression of nerve roots outside from the vertebral canal. Moreover, the case of vertebrobasilar stroke upon oxygen-ozone therapy, for the treatment of lumbar disk herniation⁷ may be caused by gas emboli^{8,9}. Interestingly, Corea et al⁷ reported textually that the SIOOT, of which many of us are active members, “forbids the use of such devices for intravenous infusions because of the high risk of air embolism”.

For example, using a dosage of 20 ml would mean adopting an “out of protocol” approach. This can occur if considering a dose at least 10-20 times higher than recommended by SIOOT, *via* the ISS^{1,2}, i.e., 2-3 ml in the cervical region. Higher volumes are to be considered a serious hazard for the patient.

The correct procedure at the cervical level, which is mandatory for the ISS², includes the use of a 3-4 mm (27-gauge, G) or a 12.7 mm (26 G) needle for paravertebral subcutaneous injection (at 1-2 cm from the spinous process). Then, it involves the injection of 2-3 ml of an oxygen-ozone mixture (5-12 µg/ml O₃), reaching a maximum of 10 ml for side and for single intervention. At the lumbar level, for the paravertebral injections of lumbar herniation disc, SIOOT recommendations² include

a 25-30 mm (27 G) needle (50 ml syringe) for injection. Injection is performed at 2-3 cm from the spinous process, using 5-10 ml (each point) of an oxygen-ozone mixture (5-10 µg/ml O₃) reaching a maximum of 40 ml for single intervention. In both cases, it is mandatory to perform a proper aspiration to prevent the event of erroneously catching a blood vessel. Furthermore, in 50% of treated cases, the time from injection to symptoms onset was immediate, suggesting possible effects due to the approach used².

While considering that the use of ozone in various muscular-skeletal disorders and back pain is a possibility, though hazardous if not correctly performed^{10,11}, physicians who are approaching to write a paper, or a protocol should cite methods and recommendations held by assessed Scientific Societies such as SIOOT. Alternatively, they can refer to mandatory recommendations from the ISS, which were approved for the neuropathic pain *via* paravertebral injections². Actually, in 2008 the ISS approved, in a Consensus Conference, the application of the SIOOT protocol for using oxygen-ozone in paravertebral injections. The correct protocol should warrant for a positive outcome in the use of the oxygen-ozone therapy in low back pain or in herniated disk. In this perspective, Leonardi et al's evidence¹² is paramount.

Leonardi et al¹² considered 300 patients who received 4 ml (into the disc) and 8 ml (into the peri-ganglion) of an O₂-O₃ mixture (27 µg/ml O₃), matched with 300 controls receiving only a corticosteroid (1 ml Depomedrol 40 mg) and anesthetic (2 ml Marcain at 0.50%). The authors assessed the treatment outcome following six months and using a modified MacNab methodology and reported that treatment was successful in 74.3% of all patients, slightly lower than the controls (78.3%)¹².

Stating that ozone *tout court* causes encephalopathy needs caution, if protocols, methods, dosages and approved guidelines are not reported in any published document containing this statement^{1,2}.

Even when air bubbles in the cervical paravertebral soft tissues are reported¹, the reader cannot be warranted about the existence of an adverse effect from ozone as a toxicant respect to a non-standardized method. The authors may not detail properly the method used for their invasive maneuver. When occurring, lacking scientific details should be avoided, as it is paramount to enable the reader with the capability to be fully aware of the message reported¹.

Many other authors¹³⁻¹⁵ in detailing their practice enabled readers to fully realize of the possible concern with using ozone in neurosurgery. Although some authors tried to recommend some guidelines for intradiscal ozone¹⁶, paravertebral ozone therapy is consented, respect to intradiscal injection for low back pain and radiculopathies, as well as percutaneous ozone for herniated lumbar disc¹⁷⁻¹⁹. We fully criticize the statement that ozone causes encephalopathy *tout court*, as physician's expertise and handling are paramount, to earn a successful outcome.

We recently reported evidence from SIOOT with intra-muscular oxygen-ozone therapy on sixty patients suffering from acute low back pain triggered by lumbar disc herniation and recruited in a multi-center randomized double-blind controlled trial. We showed that 61% of O₂-O₃ treated patients *vs.* 33% (controls) became pain-free within 6 months following the treatment, without any adverse effect²⁰. Furthermore, the active treatment with O₂-O₃ reduced notably the use of NSAIDs at two and three months following the ozone therapy²⁰.

When considering the retrievable positive outcomes published elsewhere in the literature about the "correct" method to address low back pain due to disc herniation with ozone, we are fully persuaded those failures may also be caused by poor expertise, low professional endowment, and lacking method standardization. Physicians and radio-neurologists are highly recommended to do not adopt intradiscal ozone in a non-public and Government affiliated private structures, as procedures are forbidden by the Italian Ministry of Health². Although these maneuvers are consented in public, institutional healthcare units could perform them exclusively on a free and experimental basis, upon the patient's informed consent, who is obliged to be fully aware of the health risk associated with the iatrogenic practice. This risk includes gaseous embolism and inner hemorrhagic damages.

Therefore, our conclusion is to have caution before indicting the sole ozone as a leading cause of encephalopathy, as the way by which ozone is used is paramount to warrant safety in its clinical use.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

- 1) Haggiag S, Prosperini L, Stasolla A, Gerace C, Tortorella C, Gasperini C. Ozone Induced Encephalopathy: a novel iatrogenic entity. *Eur J Neurol* 2021; 28: 2471-2478.
- 2) Coclite D, Napoletano A, Barbina D, Guerrera D, Guerra R, Paoloni M, Santilli V, Franzini M. Consensus Conference Ossigeno-ozono terapia nel trattamento delle lombosciatalgie da ernia discale con tecnica iniettiva intramuscolare paravertebrale. *Rapporti ISTISAN* 2008; 35: 08/9 Rome Nov 20th 2006.
- 3) Tirelli U, Franzini M, Valdenassi L, Pisconti S, Taibi R, Torrisi C, Pandolfi S, Chirumbolo S. Fatigue in post-acute sequelae of SARS-CoV2 (PASC) treated with oxygen-ozone autohemotherapy - preliminary results on 100 patients. *Eur Rev Med Pharmacol Sci* 2021; 25: 5871-5875.
- 4) Tirelli U, Taibi R, Chirumbolo S. Post COVID syndrome: a new challenge for medicine. *Eur Rev Med Pharmacol Sci* 2021; 25: 4422-4425.
- 5) Giacalone A, Quitadamo D, Zanet E, Berretta M, Spina M, Tirelli U. Cancer-related fatigue in the elderly. *Support Care Cancer*. 2013; 21: 2899-2911.
- 6) Tirelli U, Cirrito C, Pavanello M, Del Pup L, Lleshi A, Berretta M. Oxygen-ozone therapy as support and palliative therapy in 50 cancer patients with fatigue - A short report. *Eur Rev Med Pharmacol Sci* 2018; 22: 8030-8033.
- 7) Corea F, Amici S, Murgia N, Tambasco N. A case of vertebrobasilar stroke during oxygen-ozone therapy. *J Stroke Cerebrovasc Dis* 2004; 13: 259-261.
- 8) Freund PR, Alshafai L, Margolin EA. Multifocal Stroke From Ozone Gas Emboli. *J Neuroophthalmol* 2019; 39: 518-519.
- 9) Judge C, Mello S, Bradley D, Harbison J. A Systematic Review of the Causes and Management of Ischaemic Stroke Caused by Nontissue Emboli. *Stroke Res Treat* 2017; 2017: 7565702.
- 10) Akkawi I. Ozone therapy for musculoskeletal disorders Current concepts. *Acta Biomed* 2020; 91: e2020191.
- 11) de Sire A, Agostini F, Lippi L, Mangone M, Marchese S, Cisari C, Bernetti A, Invernizzi M. Oxygen-Ozone Therapy in the Rehabilitation Field: State of the Art on Mechanisms of Action, Safety and Effectiveness in Patients with Musculoskeletal Disorders. *Biomolecules* 2021; 11: 356-361.
- 12) Leonardi M, Simonetti L, Raffi L, Cenni P, Barbara C. Mini-invasive treatment of herniated disc by oxygen-ozone injection. *Interv Neuroradiol* 2003; 9: 75-83.
- 13) Andreini I, Arrigucci U, Monti L, Bellini M, Battisti C, Federico A. A case of pneumocephalus as complication of ozone therapy: diagnosis and treatment. *Neurol Sci* 2020; 41: 481-483.
- 14) Scassellati C, Galoforo AC, Bonvicini C, Esposito C, Ricevuti G. Ozone: a natural bioactive molecule with antioxidant property as potential new strategy in aging and in neurodegenerative disorders. *Ageing Res Rev* 2020; 63: 101138.
- 15) Molinari F, Simonetti V, Franzini M, Pandolfi S, Vaiano F, Valdenassi L, Liboni W. Ozone autohemotherapy induces long-term cerebral metabolic changes in multiple sclerosis patients. *Int J Immunopathol Pharmacol* 2014; 27: 379-389.
- 16) Giurazza F, Guarneri G, Murphy KJ, Muto M. Intradiscal O2O3: Rationale, Injection Technique, Short- and Long-term Outcomes for the Treatment of Low Back Pain Due to Disc Herniation. *Can Assoc Radiol J* 2017; 68: 171-177.
- 17) Bhatia A, Munk P, Lee D, Elias G, Murphy K. Percutaneous Ozone Treatment for Herniated Lumbar Discs: 1-Year Follow-up of a Multicenter Pilot Study of a Handheld Disposable Ozone-Generating Device. *J Vasc Interv Radiol* 2019, 30: 752-760.
- 18) Melchionda D, Milillo P, Manente G, Stoppino L, Macarini L. Treatment of radiculopathies: a study of efficacy and tollerability of paravertebral oxygen-ozone injections compared with pharmacological anti-inflammatory treatment. *J Biol Regul Homeost Agents* 2012; 26: 467-474.
- 19) Magalhaes FN, Dotta L, Sasse A, Teixera MJ, Fonoff ET. Ozone therapy as a treatment for low back pain secondary to herniated disc: a systematic review and meta-analysis of randomized controlled trials. *Pain Physician* 2012; 15: E115-E129.
- 20) Paoloni M, Di Sante L, Cacchio A, Apuzzo D, Marotta S, Razzano M, Franzini M, Santilli V. Intramuscular oxygen-ozone therapy in the treatment of acute back pain with lumbar disc herniation: a multicenter, randomized, double-blind, clinical trial of active and simulated lumbar paravertebral injection. *Spine (Phila Pa 1976)* 2009; 34: 1337-1344.