Review

MEDICAL OZONE TREATMENTS. THE GOOD, THE BAD, AND THE UGLY

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ABSTRACT

Although medical ozone treatments are becoming increasingly frequent, there is still a lack of information regarding complications or adverse effects. Medical ozone is a valuable therapeutic resource when used appropriately and under the supervision of qualified doctors. It is essential that physicians utilize medical ozone within their respective medical specialties. We must abandon the notion that ozone has no adverse effects or complications. A few cases of complications related to ozone are described in the scientific literature index. Some papers deal with actual complications, but others are biased and misinformed. We have analyzed the most popular and controversial papers to reach a conclusion. It is time for the entire medical community to start sharing their experiences, including both successes and failures. This is the only way to advance and continue learning for ozone to be considered as the valuable therapeutic resource that it is.

KEYWORDS: *ozone, therapy, chronic oxidative stress, chronic inflammation*

INTRODUCTION

Medical ozone remains controversial in medicine. Bad press, fear, and, of course, confusion regarding ozone in nature and its effects on the airways. Investigation has been very successful in the last decades, and it has been recognized within the scientific community. Medical ozone has been used since the XIX century, yet many physicians all over the world are still unaware of its existence. That is why in 2022 Yaziciouglu et. concluded that the knowledge and attitudes of healthcare professionals towards ozone therapy are not satisfactory (1). However, it cannot be denied that papers arise daily with experimental models, case reports, reviews and trials about medical ozone, which give doctors enough evidence to be able to use in their specialty.

Nevertheless, medical ozone is not exempt from complications, which are frequently due to misuse or incorrect diagnosis and/or prescription. Now is the time to clarify that medical ozone is not toxic when used in the correct doses and indications and in the proper medical hands. Like any another medical resource, it must be used and prescribed by

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doctors. In this paper, we review reported complications with medical ozone since 2000 in indexed bibliography, and we discuss whether these complications were due to medical ozone or some other cause.

A piece of history

Ozone, a gas discovered in the mid-nineteenth century, is a molecule consisting of three atoms of oxygen in a dynamically unstable structure due to the presence of mesomeric states (2).

Medical ozone applications date back to the beginning of the last century. Dr. Kellogg, in his book on diphtheria (1881), already mentioned ozone as a disinfectant, and in 1898 Dr Thauerkauf and Dr Luth founded the "Institute for Oxygen Therapy" in Berlin, carrying out the first trials with animals. In 1911, the book "A Working Manual of High Frequency Currents," published by Dr. Noble Eberhart, head of the department of physiological therapeutics at Loyola University, described the use of medical ozone in the treatment of different diseases (3).

Starting from the late 1970s, medical ozone has had great development all over the world, thanks to the refinement of administration techniques and protocols, and to the collaborative work of some European medical societies. This contributed significantly to the set-up of regulatory requirements for ozone application, including the production of medical ozone, the use of appropriate disposable materials, and the definition of concentration, dosages, and treatment frequency in relation to the disease (4).

Airways and medical ozone

The main reason for the toxicity is due to the cumulative ozone dose that, day after day, elicits the formation of noxious products. This fact has established the dogma that ozone is always noxious, so its medical application should be forbidden. This dogma has been reinforced by prejudice and lack of knowledge of the mechanisms of action of ozone. Almost everyone living in polluted cities knows that ozone, present in the photochemical smog, should not be breathed and that its continuous inhalation damages the respiratory system and extrapulmonary organs. Chronic oxidative stress established by ozone in the lungs causes a steady release of a huge amount of peroxidative products and proinflammatory cytokines which, after overwhelming the antioxidant defenses, enter the circulation and cause chronic inflammation in several organs (5).

Routes of administration

Except for the inhalation route, there are many parenteral and topical routes to the administration of medical ozone. The most popular are described in Table I.

Table I. *Parenteral and topical routes to the administration of medical ozone.*

Routes of administration
Major blood ozonation (MBO)
Minor blood ozonation (mBO)
Rectal insufflation (RI)
Intramuscular (IM)
Subcutaneous (Sc)
Intra-articular
Intralesional
Intradiscal (ID)
Intraforaminal
Intraperitoneal
Urethral and intravesical
Vaginal
Hyperbaric MBO
Topical
Ozonated oils
Ozonated water

Neither the inhalation nor the direct intravenous route should be used under any circumstances. Most used routs of medical ozone administration are MBO, mBO, IR, IM, Sc, ID, so complications described in scientific literature are about these ones (6).

COMPLICATIONS MORE OFTEN DESCRIBED IN BIBLIOGRAPHY

Intradiscal lumbar complications

Pneumoencephalus

Pneumoencephalus is the presence of gas in the intracranial cavity. It seems to be one of the most common complications with intradiscal procedures according to bibliography.

In 2006 Chalaupka et al. (7) published a case report about a young man, who underwent medical ozone treatment for lumbar disc herniation at the L4-L5 level and about 2 minutes after the injection, he developed severe non pulsating pain of abrupt onset in the left side of his face and in the occipital area. The following day the headache was widespread, worsened by movement and accompanied by photophobia, nausea, and vomiting. The brain computed tomography (CT) scan revealed large air collection in the frontal horns of the lateral ventricles and a smaller one in the Ponto-mesencephalic region, compatible with pneumoencephalus. The patient improved with bed rest and was discharged from the hospital after 4 days.

In this paper there is no description of technique, volume, concentration or equipment. There is no information about the use of RX nor anesthesia in the procedure. It is very clear from the CT scan the presence of air. So, this was not an intradiscal injection, but an accidental intradural injection.

In 2019, in a letter to the editor, Ilenia Andreini et al. described another case of pneumoencephalus (8). In this case the technique is briefly described. However, they concluded that pneumoencephalus could be a possible complication of medical ozone. Again, this is far from true: pneumoencephalus is a complication of the punction. If they had injected ozone into the intradiscal space, pneumocephalus would not have occurred.

In 2017 Hüseyin Toman et al (9) described another case of pneumoencephalus, but this paper is very different, about a 41-year-old female patient with failed back surgery syndrome (FBSS). According to the technique described there, the process seemed to be carried out correctly. However, after the procedure, the patient developed a severe headache and nausea. A CT scan of the patient's head was performed immediately and showed air in the intracranial cavity. In this case this could have happened because in FBSS patient's lumbosacral region anatomy is altered. It is very common for post-surgical adhesions to occur after spinal surgery. This makes the approach complex and may result in an injection into the intradural cavity.

In 2017, Beyaz et al. described a case report about a patient who underwent lumbar intradiscal procedure with insertion of a Racz neuroplasty catheter. This technique consists of three injections of medical ozone planned for 3 days. The authors describe that on the first day an epidural medical ozone injection was made according to the planned protocol, but on the second day more volume was injected accidentally. Pneumoencephalus and cardiopulmonary arrest occurred. The Racz catheter could have injured the dura inadvertently and damage could have developed following the migration of the catheter from the dura to the intrathecal field and medical ozone directly reached the endocranial cavity through the intrathecal route (10). Once again, it is not correct to think that this was a complication from intradiscal medical ozone procedure. It happened because the catheter injured dura. It has nothing to do with the volume injected.

Analyzing these studies where pneumocephalus occurred, it can be understood that these were complications due to a technical error in the procedure. The needle was introduced into the spinal subarachnoid space. Ozone did not cause the complication, but rather the injection was performed incorrectly.

Acute bilateral vitreo-retinal hemorrhages

There is only one paper documented in PubMed with this complication. In 2004 Lo Giudice et al. described a case report of a 45-year-old woman who underwent an intradiscal procedure (11). Although a brief description of the technique was made, neither anesthesia nor XR were used. After the procedure the patient noticed "patches" obscuring her vision in both eyes. The authors concluded that intraocular hemorrhages after ozone intradiscal injection could be considered a complication. This is false. The complication was the injection of ozone into the subarachnoid space due to the abrupt and transient increase in intracranial pressure.

Neurological symptoms

In 2004 Corea et al. wrote the most cited paper by the detractors of medical ozone. They described a case report about a 66-year-old woman with hypertension, who was admitted at the hospital with bilateral blindness. The patient

developed a tension type frontal headache and sudden bilateral blindness during a lumbar intradiscal ozone injection. Neurologic examination showed amnesia, disorientation, delirium, among other symptoms.

A CT scan immediately after the onset of symptoms showed multiple lacunar lesions, but no sign of recent ischemic or hemorrhagic stroke. Magnetic resonance images (MRI) showed hyperintensities in various parts of the brain, but magnetic resonance angiography was normal. Duplex ultrasound examination revealed a slight bilateral reduction of diastolic signal in vertebral arteries. Three days later the patient experienced tonic-clonic seizures and electroencephalography showed sporadic left parieto occipital paroxysmal activity. The patient was discharged 10 days later with antiepileptic and aspirin treatments.

Authors concluded that cortical blindness is the result of basilar hypoperfusion which is generally determined by embolism or a thrombus, but in this case, angiography was normal. They also hypothesized that pain during the ozone injection performed without X-ray nor anesthesia could have provoked arrhythmias leading to migration of thrombotic debris from cardiac chambers. This hypothesis could not be proved.

They ruled out the possibility of intravenous gas injection because they found no abnormalities in the cardiac studies. They also ruled out a possible toxic effect of ozone because they assume that the concentrations and volumes used were low. However, this is not the only report about encephalopathic syndrome (stroke like) after ozone injection. In other case reports, medical doctors have found patent foramen oval (POF) and accidental ozone injection into epidural venous region, which does not seem to be so impossible. In this case, it is not POF described, so, it could be possible that medical ozone provoked irritation and vasogenic edema. However, there are too many questions. The procedure was carried out without Xray, and without anesthesia, so doubt remains where the needle was placed (12).

In December 2024, Sepehr Khosravi and Zahra Mirzaasgari published a case report of another stroke after lumbar intradiscal procedure. The patient had an acute onset limb weakness and speech disturbance that happened during a lumbar intradiscal ozone injection session. Then, when brain CT and MRI scans were done, they showed multiple cerebral gas embolisms and diffusion-restricted areas in both cerebral hemispheres. Echocardiography revealed a patent foramen oval (POF), hinting at a conduit for paradoxical embolism. The presence of POF is a common factor when post-intervention neurological effects are seen. Despite this paper, there is a lack of information about how the procedure was done, it is very important to take account of this kind of adverse effect (13). Later, in this paper we will discuss other cases of stroke post paravertebral medical ozone.

Cortical blindness (CB) is a neurological syndrome characterized by bilateral visual loss in the context of normal pupillary function, extraocular eye movements, and fundoscopy results. This syndrome is often associated with ischemia of the visual cortex, head trauma, migraines, hypertensive encephalopathy, and many other lesions of the visual cortex. If the lesion extends beyond the striate cortex into the visual association area, patients with CB may exhibit anosognosia (also known as Anton's syndrome, in which the patient may deny blindness) (14).

In 2016 Vaiano et al. wrote a case report about a patient who was presented with acute blindness one minute after an intradiscal injection of medical ozone (volume and concentration seems to be correct). After five minutes, it was followed by severe frontal headache, vomiting, and nausea. A CT scan performed two hours after the onset of visual loss and headache symptoms showed no signs of an acute ischemic lesion or hemorrhagic stroke. Two days later, brain MRI revealed multiple areas of hyperintensity on T2 sequences and diffusion-weighted images. He recovered 10 days later.

Transcranial Doppler emboli detection with contrast saline showed the presence of ten micro embolic signals. Transesophageal contrast echocardiography revealed the presence of PFO, and atrial septal aneurysm associated with the detection of early microbubbles in the left atrium during Valsalva release.

There was no evidence of a clot associated either with the atrial septal aneurysm or anywhere in the heart. According to MRI data, the CB was caused by recent ischemic lesions in the bilateral posterior cerebral artery's vascular territories. This ischemia is generally due to a mechanism of embolism or hypotensive episode.

The authors support air embolism as the most likely cause of cortical blindness. It is well accepted that PFO is highly prevalent in patients with cryptogenic stroke. It is possible that the injection in the lumbar region occurred in a vascular bed and that the embolism was caused by the POF. All the evidence indicates that it was air embolism (15).

Myocardial infarction

He R. et al. reported a female without heart disease history who underwent lumbar intradiscal injection and after the procedure she complained of weakness and bilateral loss of sensation in the lower limbs. Therefore, it can be inferred procedure was done without anesthesia. The neurological exam demonstrated complete flaccid paralysis of both lower extremities and absence of deep tendon reflexes. Sensation to pinprick and temperature were impaired below T4 level. Just a few minutes later, she complained of acute chest pain. Three days later MRI revealed hyperintensity in the thoracic cord from T2 to 10 level.

Computed tomography angiography (CTA) disclosed no aortic disease nor vertebral stenosis, but transthoracic echocardiography with saline contrast showed a right-to-left shunt with massive micro embolic signals in the left atrium during the resting state and Valsalva maneuver indicating the presence of a large POF. Vascular ultrasound did not detect venous thrombosis in the four extremities. Therefore, she was diagnosed with anterior spinal cord syndrome and ST-elevation myocardial infarction (STEMI), and it was attributed to air embolism.

It is very common that lumbar intradiscal ozone injection is performed in prone position. As we have said before, there is a vast vascular bed in epidural region, so it could be very possible to do injection on a vein. The accident is most probably caused by air embolus produced by ozone injection on venous system and because of POF subsequently entered arterial circulation. It is important to consider that the procedure was done without anesthesia and prone position (which could increase abdominal pressure). The accident was caused most probably by air embolus produced by medical ozone injection and subsequently entering in arterial circulation (16). It is necessary to start to think about screening the patient for right-to-left shunt prior to intradiscal medical ozone.

Infection

Fort et al. describes a very controversial case report of a young woman with a 5-month history of back and leg pain because of disc herniation. Previously, the patient had been treated with acupuncture, trigger point injections, trochanteric injections, facet radio frequency neurolysis, and a percutaneous intradiscal ozone injection. Before ozone injection, MRI showed disc herniation, and after the procedure, the patient had worsened. Lab test showed leukocytosis (data not shown in paper), and a subsequent MRI illustrated L5–S1 disc space collapse with soft tissue swelling, and the authors assumed it was consistent with discitis. However, open biopsy yielded no growth in culture mediums.

Even though antibiotic treatment with 4 weeks of intravenous vancomycin and ceftriaxone was initiated, without symptomatic relief. Four months later, the patient presented decreased muscle strength and hyperesthesia in the lower extremities. Computed tomography and magnetic resonance imaging examination depicted severe disc degeneration, vertebral body endplate changes at L5–S1, and paravertebral soft tissue swelling compatible with a previous infection, according to the authors speculations.

The patient underwent surgery and instrumentation at L5–S1. Intraoperatively, significant scarring surrounding the iliac vein and peridural fibrosis were encountered without evidence of pus or necrosis. Histopathological evaluation confirmed chronic osteomyelitis and septic discitis at L5–S1. Intraoperative cultures grew A. xylosoxidans (disc material) and Propionibacterium acnes (epidural space). The patient received 6 weeks of antibiotics without complications and achieved complete symptomatic resolution without constitutional signs of infection (17).

Let us analyze this case report. In the first surgery in the extracted material no growth was observed, however the patient received intravenous vancomycin for a month. We believe that there was a misinterpretation of the initial MRI. When Modic changes are severe, they can be confused with discitis. The patient presented leukocytosis, but the authors did not state the value or the prevalence of leukocyte populations. Leukocytosis can occur in many inflammatory situations. In the second intervention, growth of p. acnes (typical of Modic changes) (18, 19) and A. xyloxidans, which is typical of intravenous fluids, was obtained. This could happen due to the month of intravenous vancomycin.

A. xylosoxidans is a rare opportunistic pathogen not usually isolated in the normal human flora but known to contaminate humidifiers and intravenous fluids. A. xylosoxidans infections are most commonly attributable to nosocomial acquisition, such as indwelling catheters or contaminated solution, and occur in patients with a predisposing illness (20, 21).

Intradiscal cervical ozone injections

There are very few cases of complications in cervical intradiscal injections, and all of them are infections. In 2009 Bo et al. published a case report about a woman with multilevel disc herniation treated with ozone without prophylactic antibiotic therapy. After ozone injection, the patient started with fever and progressive quadriplegia. The MRI revealed a homogeneously enhancing anterior epidural collection extending from C1–C4 resulting in anterior compression of spinal cord, as well as homogeneous enhancement in part of C3/4 disc linked with the epidural lesion. An empirical broad-spectrum antibiotic intravenously was initiated. She was diagnosed with pyogenic discitis secondary to ozone injection for cervical disc herniation. S. bovis was isolated from the epidural infected tissue whose usual port of entry is the colon. The most common route for the spreading of infection to cervical spine is through a hematogenous seeding. However, this route was ruled out in this case since no infectious organism was identified in the blood.

The authors concluded that the most likely pathophysiological mechanism was direct inoculation of the bacteria by iatrogenic injections. It is very clear that the lack of sterility was the problem here, not medical ozone. However, this prestigious journal published this article with a very biased title condemning medical ozone (22).

Andres Cano et al. in 2016 described a female patient who had sepsis secondary to spondylodiscitis. According to authors this was a consequence of cervical intradiscal ozone injection. Patient had fever and neck tenderness without neurological deficit, leukocytosis, and elevated PCR. MRI revealed extensive spinal epidural abscess and cord compression. Access and drainage of the wide prevertebral abscess were performed using a standard right-sided anterior cervical approach. Beta-hemolytic streptococcus was isolated from the epidural infected tissue so a transesophageal puncture during disc medical ozone was suspected. The patient was treated with antibiotic therapy according to local protocol (23).

Yant et al. published the following case report in 2018. A woman who was diagnosed with cervical disc herniation received a percutaneous intradiscal ozone injection and three days later she developed fever and leukocytosis with neutrophilia. Later she started with numbness and weakness in her right upper and bilateral lower extremities as well as urinary retention. Cervical MRI revealed an increased soft tissue density along the entire extent of the prevertebral region of the neck with hyperintensity in the spinal cord from C2 to C7. One week later, enhanced cervical MRI revealed an extensive spinal epidural abscess extending from C2 to C6 anterior to the spinal cord, spinal cord myelopathy from C3 to C6, and a prevertebral abscess. She underwent surgical drainage and culture revealed growth of Streptococcus intermedius.

The authors concluded that the most likely route of infection was transesophageal puncture during the procedure. Streptococcus intermedius is native to the mouth, nasopharynx, and esophagus (24). It seems to be very clear that a major complication in cervical intradiscal ozone injection is transesophageal punction. But, once again, the medical ozone is not responsible for that. Intradiscal cervical procedures must be done by a neurosurgeon or orthopedic with spine specialty, with Xray guidance, anesthesia and cardiology monitoring. Prophylactic antibiotic therapy must be done.

Major blood ozonation (MBO)

MBO is the procedure by which a specific volume of blood is withdrawn from a peripheral vein, then exposed to medical ozone for a few seconds/minutes (according to the device used) and re-transfused by the same intra venous route in the donor (6).

In 2000 Marchetti et al. published in The American Journal of Forensic Medicine and Pathology, one of the most polemic papers in medical ozone world. A very young woman who had psoriasis suddenly lost consciousness during her 31st medical ozone treatment by major blood ozonation. Resuscitation was unsuccessful. The chest radiography and autopsy revealed that death was caused by a paradoxical air embolism. This patient had a patent foramen ovale. In this case, we have a patient who had been doing MBO 30 times before this event. We can hypothesize that on the 31st time there was a problem with the technique. The patient had had her POF since she was born, therefore this is not the cause. POF could trigger the patient's death because something was wrong with the procedure. Perhaps the blood flux was not cut in the correct moment and some air got into the system. Another question must be asked: was it really MBO the cause? We dare to question this because some medical doctors use direct infusion of medical ozone. This practice is not approved or considered by the WFOT and most experienced medical doctors (25).

If we must quote one controversial paper, it is the one from Üreyen et al. From the title to the conclusions, it is an unfounded criticism of medical ozone. They discussed a case about a young man who arrived at the emergency department at midnight coursing an acute inferior myocardial infarction. He underwent primary percutaneous coronary intervention.

Coronary angiography demonstrated a vasospasm of the left main coronary artery and proximal segment of the left anterior descending artery. Furthermore, a thrombotic total occlusion was ascertained in the right coronary artery. In the questioning, the patient mentioned that he had undergone medical ozone autohemotherapy that morning the authors concluded that medical ozone was responsible for patient's infarction more than 12 hours later.

The authors recommended to the patient to "keep away from medical ozone" because it could be the possible cause of his heart attack (26). Fortunately, medical doctors from ozone community replied to this paper in a letter to editor in 2016, in the same journal (27). Re et al. pointed out that this paper does not give any information about the technique. But there is something worse, Üreyen et al. made a huge mistake by quoting Bocci's paper where he refers an in vitro experiment, reaching wrong conclusions. Finally, it is not easy to explain how a thrombotic lesion could be produced.

Tang et al. in 2017 described a case report about a woman who arrived at the emergency department with sinus arrest with junctional escape beat rhythm and T wave tip.

The patient had diabetes and hypertension treated with drugs. After the clinical and lab test, hyperkalemia was found to be the cause of sinus arrest. The patient had no previous history of taking drugs with potassium or history of trauma that could cause metastatic hyperkalemia by damaging tissue. However, this patient had been diagnosed with chronic kidney disease half a year before. She had been receiving MBO to treat hypertension and diabetes for 9 days prior

to admission. There are no details about the technique, but authors concluded that autohemotherapy is equivalent to the input of red blood cells in vitro, so MBO may aggravate renal insufficiency and induce elevated serum potassium in patients with chronic renal insufficiency. This is not true. Technically it was not ozone but autohemotherapy alone (28).

Another case reported by Bingham et al. presents controversy due to lack of data and confusion of the authors about bibliography of ozone. They present a woman with Lyme disease and cervical degenerative disc disease who went to receive MBO. After a few minutes she went to the bathroom and lost consciousness. She was taken to the emergency department with sinus tachycardia. She admitted having had intermittent and nonspecific chest pain. On questioning she denied any cardiac history. ECG revealed a normal sinus rhythm, with no signs of ischemia or prolonged QT interval and clinical examination was normal. Toxicology exams were positive for opiates because she was medicated with these drugs. Troponin was elevated and continued to rise until 7 hours later, when it began to decline. She was diagnosed with non-ST myocardial infarction. An echocardiogram revealed apical akinesis and an ejection fraction of 53%, with no other abnormalities noted. After this, she underwent cardiac catheterization, which revealed no atherosclerotic disease or angiographic abnormalities.

Because of the patient's negative cardiac catheterization, down-trending troponin levels, and no concerning features on the ECG, the patient was discharged. When a patient suffers from syncope, the differential diagnosis is broad, and in this case, the authors included pulmonary embolism due to coagulopathy, gas embolism (because ozone is a gas), anemia due to blood extraction for therapy, cardiac dysrhythmia, occlusive myocardial infarction and oxidative stress to myocardium secondary to ozone. The problem with this paper is that the authors stated that "literature regarding ozone is scant" and "multitude of studies have shown that ozone can have hazardous effects on human health, even when present as air pollution".

Firstly, literature is not scant, and they justified their conclusion with environmental ozone papers. They mentioned oxidative stress without considering that medical ozone used in MBO has the opposite effect: antioxidant. This is a serious mistake because authors justify their conclusion using papers that talk about environmental exposure to ozone, that is, through inhalation. Lastly, authors did not consider the diagnosis of broken-heart syndrome (Tako-tsubo cardiomyopathy), which is usually the result of severe emotional or physical stress etc. This condition is also called stress-induced cardiomyopathy or broken-heart syndrome. It generally appears in women over 50 with few cardiovascular risk factors. It is characterized by retrosternal oppressive chest pain accompanied by vegetative symptoms; electrocardiographic alterations and elevation of the enzymes of myocardial injury are only found in 50% of the patients.

The electrocardiogram and echocardiography show transient abnormalities that disappear after overcoming the acute episode, and the early catetherism is generally normal, and prognosis is benign. This paper was answered by a group of medical ozone researchers highlighting all the controversial points. Mainly, authors quoted no study criticizing medical ozone and errors in the interpretation of bibliographical citations (29, 30).

Intramuscular procedures

Infections

In 2007 Spine Journal published an appalling paper about fulminating septicemia after medical ozone treatment in a man with lumbar disc herniation, who was ambulatory treated with 6 cycles of lumbar para vertebral injections of medical ozone. Fifteen days after the last cycle of medical ozone, he arrived at the hospital with a raised leukocytes number, weakness and decreased pinprick sensation. Then he became suddenly confused, tachycardic, and tachypneic, with cool pallid extremities and peripheral cyanosis. Respiratory failure led to tracheal intubation.

Abdominal and pelvic CT revealed the presence of multiple hypodense areas, air bubble-like; similar gas lesions were localized in the soft tissue and paravertebral muscles. Chest scanning showed multiple confluent areas of parenchymal consolidation bilaterally, with air bronchograms and the absence of pleural effusion, secondary to acute pneumonia. He was then transferred to the intensive care unit. Blood cultures isolated *Escherichia coli*. The patient died a few hours later with the diagnosis of sepsis secondary to disseminated infection by E. coli. Autopsy confirmed acute bilateral pneumonia and paraspinal muscle abscess, with positive results for E. coli.

Authors concluded that the most likely pathophysiological mechanism in this case was direct inoculation of the bacteria during the procedure and acute fatal septicemia should be considered among the "major complications of medical ozone" in the treatment of a herniated lumbar disc. We agree that in this case there was an infection due to inadequate asepsis of the area, but it does not mean that sepsis is a complication of medical ozone infiltrations. In any case, infections can be a complication of any type of infiltration (31).

The medical ozone community also answered this paper (32, 33) and, afterwards, the authors literally suggested that the lack of sterility during the ozone application or contamination of the gas mixture was most likely to be blamed

for the sepsis and they would like to make clear that they did not relate the patient's death directly to the ozone but assume a lack of sterility during the procedure. However, Spine's article does not suggest that. Starting with the title of this paper, it suggests that ozone was responsible for the patient's death (34).

An article with similar characteristics was published in 2014, where a woman went to the emergency room for acute lumbar pain two months after performing 6 cycles of paravertebral ozone injections. Laboratory tests showed an increase in leukocytes and CRP.

An ultrasound showed the presence of a lesion along the paravertebral musculature and a CT showed a lesion along the left iliopsoas muscle and a right paravertebral mass with similar characteristics to an abscess. Two drains were placed, and the material obtained in the puncture was sent for culture and antibiogram. The result of the cultures was staphylococcus aureus. Once again, lack of sterility is responsible for the infection, not medical ozone (35).

Another paper about a man admitted to the hospital due to pain and warmth with swelling at his left knee. He did not have another condition, but he had been treated with intra-articular ozone for gonarthrosis at the doctor's office. After this procedure he suffered from acute pain. His doctor prescribed a non-steroidal anti-inflammatory drug without improvement. So, he went to the emergency room where he was examined. He presented pain with decreased range motion and marked an increase in joint temperature besides redness and swelling of his left knee. He was diagnosed with septic arthritis, and the culture of the aspirates yielded P. aeruginosa.

This microorganism is commonly seen in immunocompromised patients, intravenous drug abusers, patients who have suffered traumatic events or in those undergoing invasive procedures. Anyway, this complication is once again because of the incorrect antisepsis of the area (36).

Encephalopathic syndrome

A young man with cervical radiculopathy and pain, who had been receiving intramuscular ozone injections in his right arm and cervical paravertebral spaces, was treated with C6–C7 anterior cervical decompression and fusion but continued to suffer from pain. According to the paper he received approximately 15 ozone injections per visit. In the last one he lost consciousness during the last paravertebral injection and had dysarthria, aphasia, right-sided weakness, and horizontal diplopia.

Urgent CT and CT angiography of the brain and neck demonstrated intra-arterial air within the right vertebral artery and multiple foci of gas throughout the fascial planes in the posterior neck. Brain MRI demonstrated multiple punctate foci of restricted diffusion involving numerous structures supplied by the posterior circulation. Neurological examination demonstrated right hemiparesis, right-sided sensory impairment, left-sided ataxia, dysarthria, dysphagia, left sixth nerve palsy with mild left seventh nerve palsy, and cognitive impairment. Fifteen ozone injections in the cervical paravertebral area, even when the concentration of ozone used (which is not specified here) was low, constitute a very high amount of ozone to cervical area. This complication is due to poor implementation of the technique. Arterial gas emboli can cause significant morbidity and mortality with intra-arterial gas volumes as little as 2 mL (37).

In the last few years, it has been described as a syndrome post paravertebral ozone injection. It is like encephalopathic syndrome and could be interpreted as stroke. Most patients had in common paravertebral ozone injections, and all of them started with dizziness, slurred speech, tingling in the extremities, and visual loss, which developed after receiving a paravertebral medical ozone. The MRI did not immediately show any acute injuries. However, 72 hours (or maybe more days) later, brain images showed ischemic lesions. Some patients suffered a tonic-clonic seizure besides cortical blindness. Brain SPECT scans showed hypoperfusion in various areas (38, 39).

In a letter to the editor, Nociti et al. described a case of posterior reversible encephalopathy syndrome following intramuscular cervical ozone injection. Symptoms include headache, nausea, vomiting, global amnesia, temporal disorientation, and bilateral cortical blindness. The head CT angiography was negative for major vessel occlusion or ischemia, while MRI showed posterior vasogenic edema. A second brain MRI evaluation performed 14 days later showed a complete resolution of the initial alterations. A neurologic evaluation showed normal visual-spatial perceptive functions. The patient was discharged with the indication of a further outpatient neurologic evaluation, which confirmed complete clinical remission (40).

More recently, Marin-Medina et al. presented a 71-year-old woman with severe complications after paravertebral cervical medical ozone (41). After the medical examination, she was diagnosed with a stroke. The initial CT scan did not detect acute ischemic areas, but extensive emphysema in the neck was observed, along with multiple air bubbles dissecting the neck muscles and surrounding the V2 and V3 segments of the vertebral arteries. A CT angiogram revealed a small aneurysm in the C7 segment of the right internal carotid artery and hypoplasia of the left communicating artery and vertebral artery, with no evidence of stenosis or occlusion. A CT perfusion suggested hypoperfusion without evidence of

core infarction. The initial brain MRI revealed small lesions, but a subsequent brain MRI demonstrated extensive edema surrounding the previously described lesions, accompanied by small areas of hemorrhage.

Air bubbles in and around the cervical arteries, as seen in this patient, have been observed in patients with cervical paravertebral ozone injections, suggesting a direct passage of ozone into the arterial circulation, although the precise pathophysiology is not completely understood. The author quotes a recent paper which has provided evidence that mobile bubbles within small vessels can lead to the formation of thrombi, contributing to circulatory occlusion (42).

DISCUSSION

Pneumoencephalus, one of the most common complications in lumbar intradiscal procedures, is obviously an accidental punction out of the disc, in intradural space. This is a human mistake, not a medical ozone complication. Infection is an unwanted effect of any medical procedure: injection, surgery, dental procedure etc. It is incorrect to attribute this kind of complication to medical ozone.

We cannot deny that the reports describing neurological complications such as encephalopathic syndromes and stroke are the most worrying. At the same time, we cannot ignore the fact that many papers do not have enough data nor descriptions about methods to reach a certain conclusion. However, according to the bibliography analyzed (12, 13,15,16) most of neurological complications after lumbar intradiscal procedures were produced in patients who presented POF (three of the four papers).

The case report presented by Corea et. al. does not describe POF but we really do not know if this situation was really analyzed or considered in this patient (12). So, we cannot rule it out. We cannot forget that medical ozone is a gas, so maybe it is important to screen patients to determine if they have a POF before doing any procedure with ozone just in case. When this collateral unwanted effect was described in paravertebral procedures (37, 38, 39, 40), we saw that in 3 of them it was cervical (37, 39, 40).

The other paper lacks a lot of information, one of the patients does not even know which region of the spine was treated and in the other patient it was injected in the shoulder near the cervical spine. In these cases, the most probable conclusion, and even described by different authors, is that it could have occurred vasogenic edema (three of the four papers). In cervical spine it is essential to work with low volume and concentration, very well calibrated equipment, and to go slow in the injection to avoid vasogenic edema and eventually passage to the blood encephalic barrier.

More recent evidence indicates that maybe little bubbles of gas could pass through arteries leading to stroke related symptoms. The procedures must be done by trained and experienced doctors and, as Marin-Medina says (41), the potential for serious adverse events in medical ozone has been underestimated, especially as nonmedical centers increasingly offer medical ozone for a wide range of indications. This could be the most important contraindication.

CONCLUSIONS

Complications described in the use of medical ozone may be related to iatrogenic procedures and, in some situations, to ozone itself. They can occur using various administration routes (there are no exclusive ones).

Each specialist physician should only perform procedures for which they were trained, to reduce the risk of complications. There are many errors, lack of information and inaccurate and incorrect descriptions in the bibliography. The medical ozone community has the obligation to write, describe, read and discuss and be an attentive witness to report and answer each paper that defames the good practice with medical ozone.

REFERENCES

1. Yazicioglu B, Oruc MA, Emin Goktepe M, Ozturk O. Knowledge and Attitude of Healthcare Professionals Towards Ozone Therapy. Altern Ther Health Med. 2023 Oct;29(7):238-241
2. Di Paolo N, Bocci V, Gaggiotti E. Ozone therapy. Int J Artif Organs. 2004 Mar;27(3):168-75. doi: 10.1177/039139880402700303.
3. Hidalgo-Tallón FJ, Torres-Morera LM, Baeza-Noci J, Carrillo-Izquierdo MD and Pinto-Bonilla R (2022) Updated Review on Ozone Therapy in Pain Medicine. Front. Physiol. 13:840623. doi: 10.3389/fphys.2022.840623
4. Galiè M, Covi V, Tabaracci G, Malatesta M. The Role of Nrf2 in the Antioxidant Cellular Response to Medical Ozone Exposure. Int J Mol Sci. 2019 Aug 17;20(16):4009. doi: 10.3390/ijms20164009.
5. Bocci VA. Tropospheric ozone toxicity vs. usefulness of ozone therapy. Arch Med Res. 2007 Feb;38(2):265-7. doi: 10.1016/j.arcmed.2006.09.011.
6. WFOT's Review on Evidence Based Ozone Therapy (Version 1) WFOT Scientific Advisory Committee 2015.

7. Devetag Chalaupka F, Caneve G, Mauri M, Zaiotti G. Thunderclap headache caused by minimally invasive medical procedures: description of 2 cases. Headache. 2007 Feb;47(2):293-5. doi: 10.1111/j.1526-4610.2006.00699.x.
8. 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 Feb;41(2):481-483. doi: 10.1007/s10072-019-04062-4.
9. Toman H, Özdemir U, Kiraz HA, Lüleci N. Severe headache following ozone therapy: Pneumocephalus. Agri. 2017 Jul;29(3):132-136. doi: 10.5505/agri.2016.36024.
10. Beyaz SG, Altaş C, Sayhan H. Cardiopulmonary Arrest and Pneumoencephaly Developing after Epidural Oxygen-ozone Mixture Therapy. Anesth Essays Res. 2018 Jan-Mar;12(1):285-287. doi: 10.4103/aer.AER_142_17.
11. Lo Giudice G, Valdi F, Gismondi M, Prosdocimo G, de Belvis V. Acute bilateral vitreo-retinal hemorrhages following oxygen-ozone therapy for lumbar disk herniation. Am J Ophthalmol. 2004 Jul;138(1):175-7. doi: 10.1016/j.ajo.2004.02.059.
12. Corea F, Amici S, Murgia N, Tambasco N. A case of vertebrobasilar stroke during oxygen-ozone therapy. J Stroke Cerebrovasc Dis. 2004 Nov-Dec;13(6):259-61. doi: 10.1016/j.jstrokecerebrovasdis.2004.08.004.
13. Khosravi S, Mirzaasgari Z. Cerebral gas embolism and multifocal ischemic stroke during oxygen-ozone therapy: a case report. BMJ Neurology Open2024;6:e000885. doi:10.1136/bmjno-2024-000885
14. Kondziella D, Frahm-Falkenberg S. Anton's syndrome and eugenics. J Clin Neurol. 2011 Jun;7(2):96-8. doi: 10.3988/jcn.2011.7.2.96. Epub 2011 Jun 28.
15. Vaiano AS, Valente C, De Benedetti G, Caramello G. Transient cortical blindness after intradiscal oxygen–ozone therapy. Indian J Ophthalmol 2016; 64:944-6
16. He R, Huang Q, Yan X, Liu Y, Yang J and Chen X (2019) A Case of Paradoxical Embolism Causing Anterior Spinal Cord Syndrome and Acute Myocardial Infarction Following the Intradiscal Oxygen-Ozone Therapy. Front. Neurol. 10:137. doi: 10.3389/fneur.2019.00137
17. Fort NM, Aichmair A, Miller AO, Girardi FP. L5-S1 Achromobacter xylosoxidans infection secondary to oxygen-ozone therapy for the treatment of lumbosacral disc herniation: a case report and review of the literature. Spine (Phila Pa 1976). 2014 Mar 15;39(6):E413-6. doi: 10.1097/BRS.0000000000000195. PMID: 24384664.
18. Stirling A, Worthington T, Rafiq M, Lambert PA, Elliott TS. Association between sciatica and Propionibacterium acnes. Lancet. 2001 Jun 23;357(9273):2024-5. doi: 10.1016/S0140-6736(00)05109-6.
19. Shan Z, Zhang X, Li S, Yu T, Liu J, Zhao F. Propionibacterium acnes Incubation in the Discs Can Result in Time-Dependent Modic Changes: A Long-Term Rabbit Model. Spine (Phila Pa 1976). 2017 Nov 1;42(21):1595-1603. doi: 10.1097/BRS.0000000000002192.
20. Schoch PE, Cunha BA. Nosocomial Achromobacter xylosoxidans infections. Infect Control Hosp Epidemiol. 1988 Feb;9(2):84-7. doi: 10.1086/645791.
21. Bonis BM, Hunter RC. JMM Profile: *Achromobacter xylosoxidans*: the cloak-and-dagger opportunist. J Med Microbiol. 2022 May;71(5). doi: 10.1099/jmm.0.001505.
22. Bo W, Longyi C, Jian T, Guangfu H, Hailong F, Weidong L, Haibin T. A pyogenic discitis at c3-c4 with associated ventral epidural abscess involving c1-c4 after intradiscal oxygen-ozone chemonucleolysis: a case report. Spine (Phila Pa 1976). 2009 Apr 15;34(8): E298-304. doi: 10.1097/BRS.0b013e318195a87e.
23. Andrés-Cano P, Vela T, Cano C, García G, Vera JC, Andrés-García JA. Cervical Spondylodiscitis After Oxygen-Ozone Therapy for Treatment of a Cervical Disc Herniation: a Case Report and Review of the Literature. HSS J. 2016 Oct;12(3):278-283. doi: 10.1007/s11420-016-9500-1.
24. Yang CS, Zhang LJ, Sun ZH, Yang L, Shi FD. Acute prevertebral abscess secondary to intradiscal oxygen-ozone chemonucleolysis for treatment of cervical disc herniation. J Int Med Res. 2018 Jun;46(6):2461-2465. doi: 10.1177/0300060518764186.
25. Marchetti D, La Monaca G. An unexpected death during oxygen-ozone therapy. Am J Forensic Med Pathol. 2000 Jun;21(2):144-7. doi: 10.1097/00000433-200006000-00010. PMID: 10871129.
26. Üreyen ÇM, Baş CY, Arslan Ş. Myocardial Infarction after Ozone Therapy: Is Ozone Therapy Dr. Jekyll or Mr. Hyde? Cardiology. 2015;132(2):101-104. doi: 10.1159/000431078.
27. Re L, Rowen R, Travagli V. Ozone Therapy and Its Use in Medicine. Cardiology. 2016;134(2):99-100. doi: 10.1159/000443604.
28. Tang WJ, Jiang L, Wang Y, Kuang ZM. Ozone therapy induced sinus arrest in a hypertensive patient with chronic kidney disease: A case report. Medicine (Baltimore). 2017 Dec;96(50):e9265. doi: 10.1097/MD.0000000000009265.
29. Bingham A, Platt M. A Non-ST Elevation Myocardial Infarction Associated with Alternative Medicine Ozone Infusion. J Emerg Med. 2020 Jan;58(1):106-109. doi: 10.1016/j.jemermed.2019.09.028.
30. Re L, Rutledge DK, Erario A, Baeza-Noci J, Travagli V, Menendez S, Mollica PJ. Correcting Misinformation about the Science and Practice of Evidence-Based, Safe and Effective Ozone Therapy. J Emerg Med. 2021 Dec;61(6):799-800. doi: 10.1016/j.jemermed.2021.08.001.
31. Gazzeri R, Galarza M, Neroni M, Esposito S, Alfieri A. Fulminating septicemia secondary to oxygen-ozone therapy for lumbar disc herniation: case report. Spine (Phila Pa 1976). 2007 Feb 1;32(3):E121-3. doi: 10.1097/01.brs.0000254125.85406.6e.

32. Clavo B, Robaina F, Kovacs F, Urrútia G. Re: Gazzeri R, Galarza M, Neroni M, et al. Fulminating septicemia secondary to oxygen-ozone therapy for lumbar disc herniation: case report. Spine 2007;32:E121-3. Spine (Phila Pa 1976). 2007 Aug 15;32(18):2036; author reply 2037. doi: 10.1097/BRS.0b013e3181342f8a.
33. Leonardi M. Re: Gazzeri R, Galarza M, Neroni M, et al. Fulminating septicemia secondary to oxygen-ozone therapy for lumbar disc herniation: case report. Spine 2007;32:E121-3. Spine (Phila Pa 1976). 2007 Aug 15;32(18):2036-7; author reply 2037. doi: 10.1097/BRS.0b013e31813426fd.
34. Gazzeri R, Galarza M, Neroni M, Esposito S, Alfieri A. Letters to editor. Spine (Phila Pa 1976). 2007. Volume 32, Number 18, pp 2035–2037.
35. Menéndez P, García A, Peláez R. Paravertebral and intra-abdominal abscess due to oxygen-ozone therapy for lower back pain]. Rev Esp Cir O3rtop Traumatol. 2014 Mar-Apr;58(2):125-7. Spanish. doi: 10.1016/j.recot.2013.06.003.
36. Seyman D, Ozen NS, Inan D, Ongut G, Ogunc D. Pseudomonas aeruginosa septic arthritis of knee after intra-articular ozone injection. New Microbiol. 2012 Jul;35(3):345-8.
37. Freund PR, Alshafai L, Margolin EA. Multifocal Stroke from Ozone Gas Emboli. J Neuroophthalmol. 2019 Dec;39(4):518-519. doi: 10.1097/WNO.0000000000000754.
38. Rolán DV, Lopez MM, Cuberas-Borrós G, Cuñat JL, Hervás JV, Vilamajó AM, Escudero D. Neurological symptoms following exposure to ozone. J Neurol. 2012 Dec;259(12):2740-2. doi: 10.1007/s00415-012-6667-3.
39. Haggiag S, Prosperini L, Stasolla A, Gerace C, Tortorella C, Gasperini C. Ozone-induced encephalopathy: A novel iatrogenic entity. Eur J Neurol. 2021 Aug;28(8):2471-2478. doi: 10.1111/ene.14793.
40. Nociti V, Picarelli C, Losavio FA, Reale G, Giuliano G, Della Marca G, Tumbarello M. Posterior Reversible Encephalopathy Syndrome After Intramuscular Oxygen-Ozone Therapy. Can J Neurol Sci. 2020 May;47(3):416-418. doi: 10.1017/cjn.2020.35.
41. Marín-Medina, Daniel S, et al. “Severe Complications after Ozone Therapy-Related Stroke.” Clinical Neuroradiology, vol. 34, no. 2, 25 Jan. 2024, pp. 511–514, https://doi.org/10.1007/s00062-023-01379-8.
42. Li Z, Li G, Li Y, Chen Y, Li J, Chen H. Flow field around bubbles on formation of air embolism in small vessels. Proc Natl Acad Sci U S A. 2021 29;118(26):e2025406118. https://doi.org/10.1073/pna s.2025406118