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Article

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Corneliu Balan, Mihai Schiopu, Daniel Balasa, Corina Balan
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Ozone therapy – a rare and avoidable source of infectious pathology of the spine

Corneliu Balan[1], Mihai Schiopu[1], Daniel Balasa[1], Corina Balan[2]

1Neurosurgery Department, Clinical Emergency Hospital, Constanta, ROMANIA
2ICU Department, Clinical Emergency Hospital Constanta, ROMANIA

Abstract: Ozone therapy is considered by many as an effective therapy for spinal degenerative pathologies. Despite its possible favorable results, we present a series of serious infectious complications, clearly related to ozone therapy and their treatment. The authors discuss their results compared with the literature and advocate for prudence when recommending ozone therapy.

Injection therapy for low back pain is a technique dating from the 1970' for relieving pain from spinal stenosis and spinal disc herniation. Using a needle, corticosteroids and a local anesthetic are injected in:

- trigger points, intramuscular and ligamentous regions of the lower spine, considering that they perpetuate the pain
- facet joints, considering the facet joint syndrome, aggravated by straining and heavy bending
- epidural space in the proximity of the nerve roots.

Imaging guidance (fluoroscopy and later CT scan) ensures the correct placement of the needle with low risk of damaging nerve structures and maximizes the physician's ability administer therapy. Without imaging, the risk increases for the injection to be incorrectly placed.

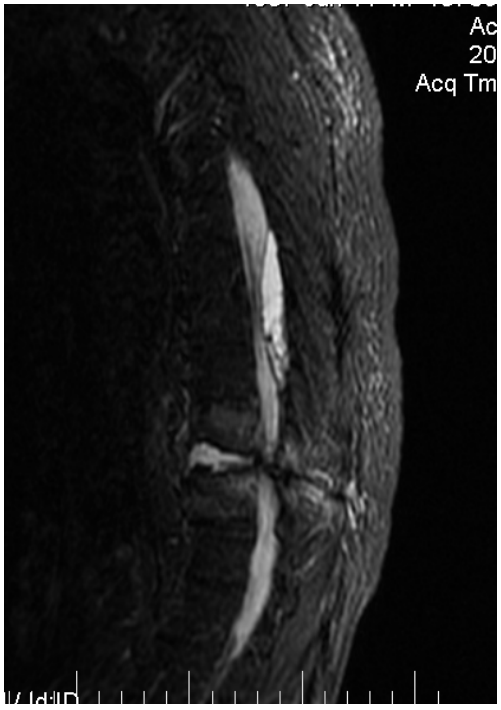
All these techniques using medication are heavy disputed among experts as they are invasive, doubly of clinical benefit in acute phase and no certified studies have adequately investigated their efficacy at 3 months. Some of them proved same efficacy as normal saline [1] and in practice guidelines are considered level III therapeutic recommendations. Despite being practiced in many countries of Europe, the FDA has not approved the use of corticosteroids for epidural injection due to the short time relief and non impact on the need for surgical intervention [2].

While the administration of classical medication is disputed, in the last 15 years there is a new trend consisting of administering ozone infiltrations, as solution, either local or intradiscal. This technique raises an even larger number of controversies given the unclear mechanism of action and high risk of complications.

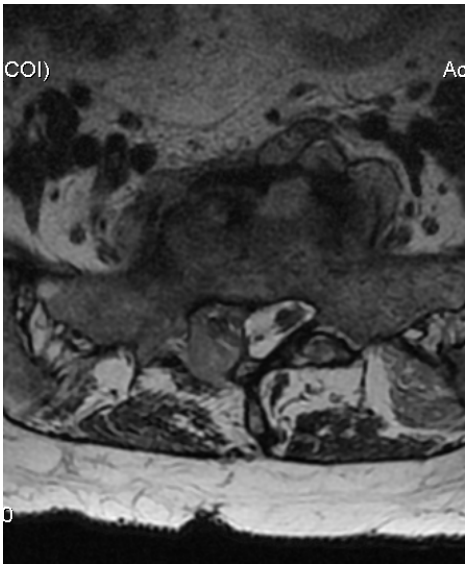
In the following paper we will present such serious complications hospitalized in the Neurosurgery Dept. of the Emergency Clinical Hospital of Constanta during the last 2 years, with the arguments of discontinuation of further ozone therapy. As summary, we dealt with 4 cases of serious spinal infections in 2 years time, in patients with no serious previous pathology, all connected with ozone therapy. Three of them were operated in our department, the fourth transferred at the patient's request then came back. All 4 required long-term antibiotics and two of them remained paraplegic, despite best medical and surgical treatment.

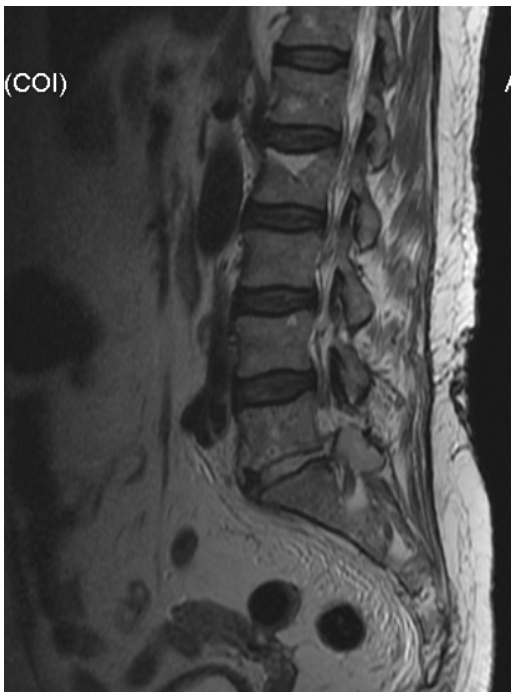
1. P.I., male, 58 yo, accused diffuse back pain located in the thoracic area for several years. After a course of balnear treatment, he was proposed by his GP, ozone therapy injected in trigger points. 12 days after the injections he started developing rapid paraparesis and was admitted in Neurology. After excluding MS with lumbar puncture and Guillan Barre syndrome, he had an MRI, almost a week since onset. On MRI several infectious lesions were discovered, as discitis, spinal epidural abscess and infection on the traject of injection. One remark is that during anamnesis he told nothing about ozone therapy.

The patient was transferred to Neurosurgery, operated – evacuation of the spinal epidural abscess by a laminectomy on 2 levels. The germ responsive was S. Aureus, sensible to multiple antibiotics. Despite adequate medical treatment, 2 months after he still presented paraparesis, with force deficit at 2/5 in lower limbs and urinary catheter.



2. C.S, female, 46 yo, known with rheumatoid arthritis for several years. She accused low back pain for several months and received injections with ozone in lumbar muscles, while being on corticoids. Almost 3 weeks after the injections, she was admitted for intense back pain, meningism, fever 38'8 C and monoparesis of the right lower limb. She received a lumbar puncture which revealed less than 50 elements/mmc but was directed to Infectious diseases. An MRI noted an abscess in the lumbar paravertebral muscles, extended in the epidural space and spondilodiscitis at C5-C6 space with small epidural and retropharyngeal abscesses. She was then transferred to Neurosurgery for surgical treatment – evacuation of the collections from the lumbar area, continued with Ceftriaxone and Ciprofloxacine for two months (S. aureus with multiple sensibilities). She had a good motor recovery despite the initial extension of the lesions.

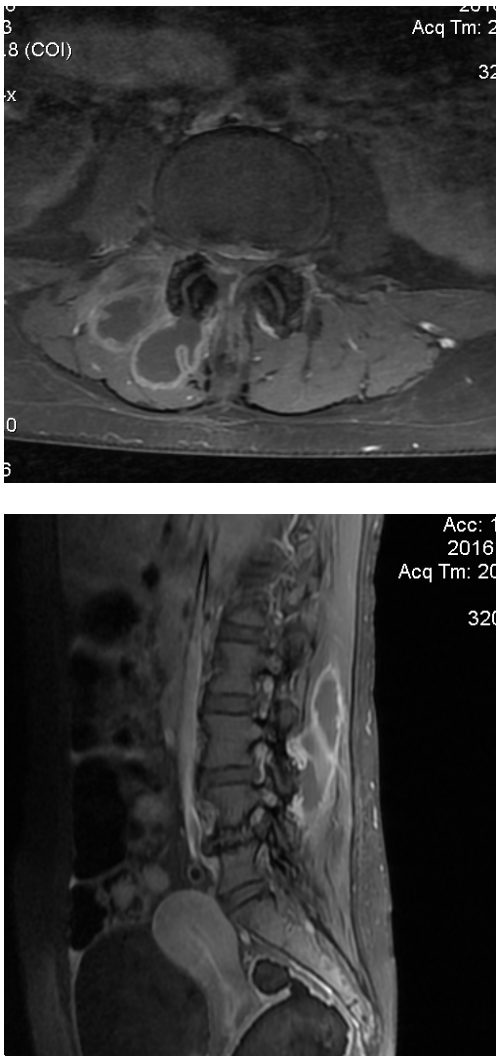




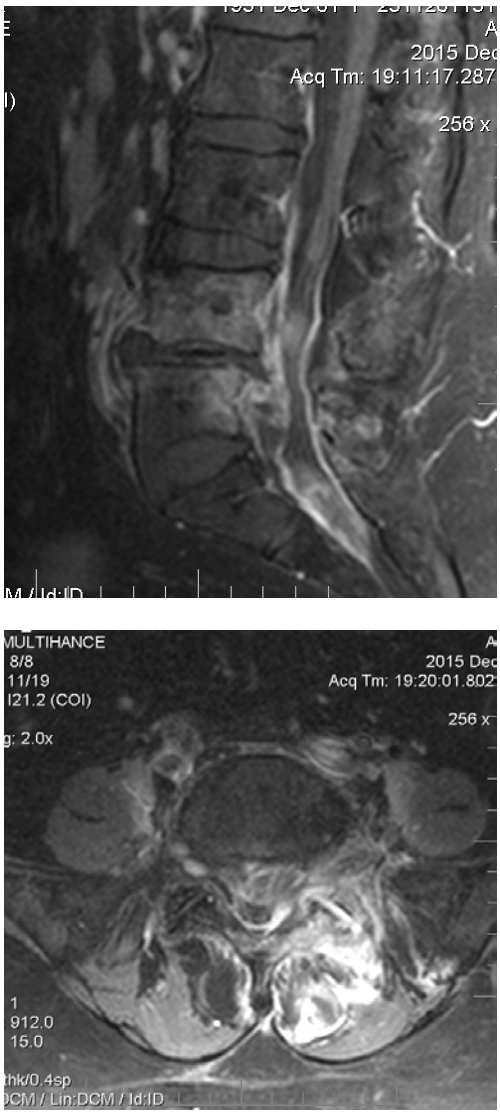
3. U.V, female, 65 yo, was admitted in Rheumatology complaining about hyperalgic lumbago, with muscle stiffness and sciatica with paresis on the right foot. The symptoms developed soon after ozone therapy realized in private practice for low back pain. After several days of treatment including opioids, she had an MRI which revealed spondilodiscitis situated at L5-S1 level, epidural and intramuscular abscess.

She was transferred to Neurosurgery and operated – evacuation of the intramuscular and epidural abscess. The germ involved was S. Aureus, sensible to Vancomicin. Clinical evolution after 2 months of antibiotherapy was favorable but one must consider she had never had any motor deficit, just pain.

4. C.L. female, 64 yo, nurse (!), with a history of 3 years of low back pain. Eleven days after an infiltration with ozone in the lumbar area she is admitted in Neurology paraplegic with acute onset in the last 2 days. MRI revealed spondylodiscitis, extended anterior and in the spinal canal as well an infection in the paravertebral muscles, left side. Her family asked for her to be transferred to another hospital in Bucharest. Operated, she had just a slight motor improvement at 4 months.



Case 3



Case 4

Facts

Ozone therapy is a non conventional technique similar to classic spinal infiltrations, consisting of injecting ozone (O3) in small doses intradiscal to realize a dehydration of the disc and diminishing intradiscal pressure and nerve compression. Another possibility is the administration intraarticular or periganglionic / periradicular areas, all under CT scan control. There are also reports of ozone injected in lytic areas of spondylolisis / spondylolisthesis. However, due to its high diffusion coefficient, in many cases where CT scan is not available, ozone is simply administered intramuscular or even subcutaneous in the vicinity of the painful area, up to 20-30 ml of gas. Some ozone therapy enthusiasts promote even ozone rectal insufflation - the introduction about a certain amount of humidified gaseous ozone that enters the bloodstream through the intestinal walls and would represent alternative therapy for hepatitis B and C, Crohn's disease, ulcers, ischemic disease, fistulas, gastritis, chronic colitis, liver cirrhosis, detoxification and premature aging.

The medical use of ozone is not licensed either by FDA or EMEA as there are yet no meta-analysis or multicentric studies to prove its efficacy. However, it is realized in some countries in Europe (France, Italy, Spain) or South America (Brazil), with local license by their national health services, mostly in private practice as high rewarding for those who realize it. In Italy, for instance, there is even "Rivista italiana di Ossigeno-Ozonoterapia" founded in 2002, with papers mainly from Italy, Spain, Cuba and Brazil [3] which evolved in 2008 as the"International Journal of Ozone Therapy" , together with a World federation for Oxygen-Ozone Therapy [4]

Production: medical ozone is obtained from pure medical oxygen to avoid the presence of toxic byproducts and other gases. Conversion is achieved with ozone generators,

close to the moment of use, due to gas lability. Most generators are still based on the Corona system created by Werner Siemens, founder of the industrial conglomerate named after him till today. The most important is to use an ozone generator suitable for a clean product, pure and uncontaminated. This is possible only when ozone reaches glass electrodes (never metal or ceramic) as still in the generator. If triatomic oxygen comes in contact with metal, plastic, rubber or other oxidizable materials, the decomposition of these materials will contaminate ozone.

Ozone is in fact, a mixture of ozone and oxygen (O3/ O2) where ozone is no more than 5% of total mixture. Richer ozone concentrations are used for intradiscal injections and accelerate disc dehydration and degenerative disc changes, decreasing compression caused by hernias. Poorer concentrations are used for regenerative responses. The oxygen/ozone mixture is highly safe with regard to toxicity, even in relatively high concentrations such as 20 to 30 μ per mL, and may be applied even when disc hernia is non contained. Some authors classify ozone therapy as the safest type of chemonucleolysis as compared to papain

Physiopathology (according to those who use it) - ozone is approximately 10 times more soluble than oxygen, the same being true for its tissue diffusion and penetration. When in contact with biologically active tissue, ozone immediately reacts with several biomolecules which, together, make up real antioxidant buffering systems. Most of these biomolecules play important anti-inflammatory and analgesic roles, simultaneously to antioxidant actions.

Ozone therapy acts on red blood cells with the formation of peroxides and metabolism activation by the glutathione system with improved oxygen release and increased tissue energy and ATP. O3 increases 2,3DPG concentration with decreased affinity of oxyhemoglobin for O2 and a shift to the left in the HbO2/Hb curve with consequent better peripheral oxygenation. Antioxidant response which follows oxidizing stimulation supplied by medical ozone is represented by the increase of substances classically known as natural anti-inflammatory, while most analgesic effects come from this response. Most pains mediated by increased muscle activity are relieved by ozone therapy as increased oxygen supply and energetic build up, translated by increased ATP concentration, give tissues metabolic protection against the anaerobic option and lower chemical stimulation to pain receptors. When combined with steroid injection, ozone therapy would have anti-inflammatory synergism which occurs in different chronologic times.

Trials and published papers – there are many reports of using medical ozone in spinal pathology - in fact most of them refer to treatment of lumbar disc hernias and spinal stenosis. We are going to present a few of them in order to offer an unaltered opinion on ozone therapy.

Trial registered as NCT00566007 [5] on The Effect of Ozone Therapy for Lumbar-Herniated Disc: Ozone is being evaluated for its efficacy infiltration and its effectiveness in comparison with microdiscectomy in the

treatment of lumbar-herniated disc with criteria for surgery. The study is currently in its phase 2 studies, which is sponsored by Kovacs Foundation. The study also evaluates the efficacy of infiltration in presence of corticoids, anesthetics, which is being compared by replacing O3 by oxygen. The study ended in 2014 after 7 years ans no results were published till now.

Bonetti and his team from Brescia, Italy have many papers published on ozone therapy. They administered ozone intraforaminally with CT guidance followed by 4 paralumbar injections weekly, on a serie of 129 elderly people with degenerative spine disease. The amelioration at 3-6 months made them conclude that ozone therapy is a safe, repeatable and innocuous treatment [3]. In another serie of 306 patients, Bonetti reported that 57.5% of 80 patients in the disc disease group treated with steroid deemed the clinical outcome to be excellent, whereas in the ozone therapy group, 74.4% of 86 patients with disc disease reported complete remission of pain [6]. In this study, differences in favor of O3 treatment were statistically significant in patients with disc disease.

In another randomized study, Gallucci et al [7] observed a satisfactory success rate with ozone-therapy combined with intraforaminal and intradiscal steroid and anesthetic injection compared to steroid alone.

Zambello et al randomized 351 patients with low back pain for treatment with either ozone or steroid (epidural) and planned a crossover during the follow-up to the other group in case of failure to respondto treatment after 4 weeks of therapy. The long-term outcome remained excellent or good in 47.3% of 171 patients treated by epidural steroid injections and in 77.1% of 180 patients treated with O2-O3 [8].

Many other authors also present favorable results on all kind of spinal degenerative pathologies when administering ozone, some in journals with important impact factor [9, 10, 11]. However, despite publishing the papers, reviewers have presented some discrepancies in the papers like those from Acta Neurochirurgica in 2016 [12,13]

Two systematic reviews of the literature, published in 2013 (Spain)[14] and 2014 (Brazil)[15], after analyzing several hundred cases conclude that the indicated level of evidence is II-3 (Evidence obtained from diagnostic studies of uncertainty) according to U.S. Preventive Services Task Force for ozone therapy applied intradiscally and II-1 (Evidence obtained from at least one properly conducted diagnostic accuracy study of adequate size) for ozone therapy applied paravertebrally on long-term relief in low back pain secondary to disc herniation. According to same studies, the grading the strength of recommendations and quality of evidence in clinical guidelines is 1C for ozone therapy applied intradiscally and 1B for ozone applied at the paravertebral muscles or periforaminally (strong recommendation, moderate to low quality evidence).

Conclusion

The data given above try to offer an impartial (if possible, as we are surgeons) view on ozone therapy, without approving or negating the results from other papers

published. As neurosurgeons, we were confronted with a large number of complications from ozone therapy, realized by several doctors, in a short period of time (4 cases of severe spine infections in less than 2 years). We don't know exactly how many patients received ozone therapy during the last 2 years nor their state of health now, as this is realized in private practice mostly. We cannot and will not evaluate the indications of other colleagues' practice, nor the quality of asepsia on injections or their competence.. However, given the already known dispute on classic infiltrations with lack of studies on efficacy of corticoids and the complications we have already seen on infiltration with ozone, we suggest, if not abstention for this new method, at least a well considered evaluation of the risks and benefits before realizing it.

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