The Italian Oxygen-Ozone Therapy Federation (FIO) Study on Oxygen-Ozone Treatment of Herniated Disc

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SUMMARY - Oxygen-ozone therapy exploits the chemical properties of ozone, an unstable allotropic form of oxygen with the symbol O₃ and a molecular weight of 48 kDa. Many biologic effects have been attributed to ozone: increased glycolysis, effects on red blood cells, effects on rheology, bactericidal, fungicide and virustatic, immunomodulating action and analgesic and anti-inflammatory effects. This broad spectrum of action explains the many indications for medical ozone administration. We assessed the results obtained in treating 15,000 patients with oxygen-ozone therapy and in particular to describe possible complications or collateral effects. The only thing we can understand is that the authors did not use correct asepsis and hygiene procedures. Hence, the low costs of oxygen-ozone therapy and the lack of any complications or collateral effects make this minimally invasive procedure safe and useful for the treatment of lumbar disc herniation.

Introduction

Oxygen-ozone intradiscal and periganglionic injection is a minimally invasive procedure first applied clinically in the peridural treatment of lumbar sciatic pain and lumbar disk herniation. A reduction in herniated disk volume is one of the therapeutic aims of the gas mixture, as disk shrinkage may reduce nerve root compression. Another reason for using medical ozone to treat disk herniation is its analgesic and anti-inflammatory effects. The transit of pure oxygen through high-voltage tubes forms ozone available for an injecting device. This type of treatment is developed to offer good clinical results combined with a well-tolerated, low-cost procedure. A vast bibliography can be found in a recent study on how oxygen-ozone works 1-3. Oxygen-ozone therapy exploits the chemical properties of ozone, an unstable allotropic form of oxygen with the symbol O₃, and a molecular weight of 48 kDa. Many biologic effects have been attributed to ozone: increased glycolysis, effects on red blood cells, effects on rheology, bactericidal, fungicide and virustatic, immunomodulating action and analgesic and anti-inflammatory effects. This broad spectrum of action explains the many indications for medical ozone administration.

We assessed the results obtained in treating 15,000 patients with oxygen-ozone therapy and in particular to describe possible complications or collateral effects.

Methods

In 2004 the FIO (Italian Oxygen-Ozone Therapy Federation) instituted a control study group to monitor possible adverse events occurring during treatments with oxygen-ozone therapy for discal pathologies. The tool used was the FIO website (www.webfio.it) in a private area that allows access to an electronic clinical folder where all the data concerning the type of treatment are collected and any complications discovered can be reported (figures 1, 2 and 3).

From January 2004 to December 2006, 12,000 patients were treated with a single session of oxygen-ozone therapy. All the treatments were executed following the guidelines of the Italian Oxygen-Ozone Therapy Federation (FIO).
These patients represent a consecutive series of patients who presented with lumbar disk herniation during the two years and who were judged not to be surgical candidates for clinical or anatomic reasons. Informed consent was obtained from all patients.

The injection site was disinfected in all patients and local anesthesia applied using an ethyl chloride spray. Infiltrations were done by specialist neuroradiologists. The puncture site was identified on CT scans and marked on the patient’s skin. The distance from this point to the foramen was subsequently measured (figure 4A). A 22-gauge needle was positioned inside the disc (figure 4B) and then 2-3 mm from the foraminal region (figure 5A), close to the ganglion of the affected nerve root. A 10 cm needle was typically used, but longer needles (15 cm) were occasionally needed depending on the size of the patient and the thickness of the skin layer. CT scanning was performed to check correct needle placement. O₂-O₃ was infiltrated by injecting 3 mL of the gas mixture at a rate of 25 µg/mL close to the neural foramen. The needle was then retracted a few millimeters and another 5 mL of
the mixture was injected to involve the facet joint region. CT scans were used to check the correct distribution of the gas mixture in the foramen (figures 5B and A).

The gas mixture was injected by using a polypropylene syringe with the interconnection of a millipore filter. Time for injection was 15 seconds in all. A longer time is not suitable because of the unstable condition of medical ozone whose decaying time (2 µg/mL) is after about 20 seconds. At the end of treatment patients were advised to rest in supine decubitus position for an hour.

No premedication or anesthesia was given to either group, and the procedure was performed at an outpatient facility. Selection criteria for oxygen-ozone therapy were clinical and included low back pain resistant to conservative management (drugs, physiotherapy and others) lasting at least three months, and low back pain with positive signs of nerve root involvement, with or without paraesthesia or hyposthesia, with appropriate dermatome distribution. Neuroradiologic criteria were CT and/or MR evidence of contained disk herniation, in line with the patient’s clinical symptoms, with or
Figure 3  FIO Website. This is the page where all the patients’ information is collected from different centres.

Figure 4  Treatment technique. A) Calculation of the access point and the position of the needle. B) The needle is correctly positioned inside the disc.
without disk degeneration, and residues of surgical microdiskectomy with recurrent herniation.

Exclusion criteria for oxygen-ozone therapy were neuroradiologic evidence of disk prolapse or free fragments of herniated disk, and major neurologic deficit correlated to disk disease. In these cases, the patients underwent surgical treatment. All patients underwent follow-up examinations two weeks, two months and six months after treatment to assess any complications or collateral effects. Clinical outcome was assessed six months after treatment by applying a modified MacNab method.

All operators could log in through our web site (www.webfio.it) and inspect patients’ data. These data are stored inside a password-protected area where operators can point out collateral effects and details of O₂-O₃ treatment.

Results

No early or late neurological or infectious complications have been reported following oxygen-ozone injection. In our experience we have observed only a few cases of vagal crisis resolved without resorting to medical management but maintaining the patient in the Trendelemburg position. The results are virtually the same as those of other percutaneous techniques (75-80% success rate).

Discussion

In oxygen-ozone therapy, ozone is administered in the form of an oxygen-ozone gas mixture, medical ozone, at nontoxic concentrations varying from 15 to 30 μg of ozone per milliliter of oxygen. For intradiscal administration the optimal concentration of ozone per milliliter of oxygen is 25 μg. At this concentration, ozone has a direct effect on the proteoglycans composing the disk’s nucleus pulposus, resulting in its release of water molecules and subsequent cell degeneration of the matrix, which is replaced by fibrous tissues in the space of five weeks and the formation of new blood cells. Together, these events result in a reduction of herniated disk volume which is one of the therapeutic reasons for intradiscal administration of medical ozone as disk shrinkage may reduce nerve root compression.

We emphasize a few simple precautions. It is very important to inform patients about the method adopted, reassure them and help them relax. The infiltrations should be administered very slowly, trying not to force the introduction of the gas to avoid causing pain to the patient. It is always better to inject a small amount of gas instead of causing pain and risking a vagal crisis triggered by the emotive state caused by the infiltrations, and possibly to pain which should normally be minimum or absent if the procedure is executed correctly.

We have searched the literature to find the main adverse events reported for the most common procedures for the treatment of herniated disk and any complications reported for oxygen-ozone therapy. In the last two decades, a better understanding of the spinal anatomy, function and the pain generation mechanism along with technological achievements has accelerated the development of many modalities for the treatment of low back pain. Chemonucleolysis with chymopapain, nucleo-discectomy introduced by Onik, intradiscal laser discectomy, intradiscal electrothermal therapy, chemodiscolysis with an oxygen-ozone mixture and most recently percutaneous nucleoplasty are the minimally invasive techniques developed for this aim.

Chemodiscolysis with chymopapain is based on an enzymatic dissolution of the nucleus pulposus. The herniation should be rigorously contained to avoid contact with the proteolytic enzyme and the spine contents like spinal cord, dural sac and roots. Moreover, although purified prepared enzymes are used, anaphylactic reactions could occur, especially in patients undergoing a repeat chemonucleolysis procedure with a prevalence of 17%. Other adverse effects reported in the USA to the Food and Drug Administration (FDA) include infections, hemorrhage, namely subarachnoid hemorrhage, and neurologic events with a mortality rate of 0.019%.4-12

The nucleo-discectomy introduced by Onik is called “automated” percutaneous lumbar discectomy (APLD) since it involves a mechanical probe. Working by a “suction and cutting” action for removal of the nucleus pulposus this is a minimally invasive technique. Candidates for this procedure should be carefully evaluated on the basis of precise clinical criteria and instrumental diagnosis. A study of 1146 patients treated by Onik reported two cases of discitis (0.17%), one acute hematoma of the iliopsoas muscle and in eight patients (0.7%) the disc protrusion appeared more bulky, extruded or sequestrated after the percutaneous procedure. Cases of infectious discitis after the procedure have also been referred in other studies13-18.

Intradiscal electrothermal treatment (IDET) was developed as a potential alternative therapy for patients with chronic lower back pain resulting from an internal disc disruption who failed to
improve with any of the wide variety of non-surgical treatments available. IDET involves coagulating the anulus fibrosus of the painful disc with a flexible electrode which is threaded into the disc percutaneously under fluoroscopic control. A study of 1675 patients treated reported a few cases (0.4%) of nerve root injury and another study had a case of cauda equina. A case report describes the migration of a broken intradiscal electrothermal therapy catheter tip from the disc space into the thecal sac, leading to a radiculopathy that improved after removing the catheter. A recent case study reported a complication of end-plate osteonecrosis post-IDET procedure, while another study found one patient with endplate erosion post-IDET. A further IDET study treating 79 patients with discogenic back pain reported a complication rate of 10%, and the only risk factor associated with intradiscal electrothermal therapy failure was obesity (P = 0.01) \(^{19-25}\). These complications raise serious concerns over the long-term sequelae of thermal treatment on the intervertebral disc and stress the importance of further studies and continued follow-up.

Percutaneous laser disc decompression (PLDD) is a minimally invasive technique pioneered by Choy and colleagues in 1984 for the treatment of patients with herniated disc problems. The advantage of PLDD is that it reduces the volume and pressure of a diseased disk. One study treated 3377 patients using the Nd-YAG laser and the complication rate evaluated was 0.5% (1% in the cervical spine area). Another study of 1275 patients treated reported 0.4% of infectious discitis. A further study with 178 herniated cervical discs in 93 patients treated with PLDD using the Nd-YAG laser reported only one complication (0.6%): a retro-esophageal abscess that responded to incision and drainage. A complication rate of less than 1% was referred in a study after 752 intervertebral discs procedure in 518 patients \(^{26-35}\).

Nucleoplasty was recently approved by the FDA (1999). The technique uses non-thermal ablation (coblation–controlled ablation) with a 10-20% reduction in disc volume. This action occurs through an electrode positioned in the nucleus pulposus using low temperatures (50-70°C) and achieves the same results as thermal ablations at high temperatures (150-200°C). The current data on this new technique are insufficient. Preliminary reports indicate that the technique is relatively safe, but early and long-term effects and/or complications observed with this procedure have not yet been reported \(^{36-38}\).

We emphasize that oxygen-ozone therapy is a minimally invasive procedure with positive results in more than 75% of the cases and no complications in our case histories of more than 15,000 patients. Our literature search disclosed some reports of adverse events. The first case report \(^{39}\) described a case of bilateral intraocular hemorrhages occurring...
after transcutaneous intradiscal and periganglionic infiltration of O₃O₂ for lumbar disk herniation. A 45-year-old woman was referred to the orthopedics department for an intradiscal (10 ml) and periganglionic (20 ml) injection of O₃O₂ mixture at an ozone concentration of 27 µg/ml for the treatment of lumbar disk herniation. The injections were administered by an extraspinal lateral approach at the L1-L2 level using a 22-gauge 17.78 cm spinal needle. The time for each injection was 15 seconds in all. No premedication or anesthesia was given, and the procedure was performed at an outpatient facility. At the end of the treatment the patient was advised to rest in a supine decubitus position for two hours. Immediately after the procedure she noticed “patches” obscuring her vision in both eyes. An ophthalmic examination seven days after infiltration disclosed a reduction of visual acuity. Magnetic resonance imaging of brain and spinal cord for intracranial hemorrhage was unremarkable. Blood pressure, blood sugar, full blood count, and clotting screen were normal.

The authors described literature reports of possible retinal hemorrhages during/after myelography or epidural corticosteroid injections. The invoked mechanism is that an increase in CSF pressure, transmitted through the sheaths of the optic nerve to the retinal venous circulatory system caused rupture of the retinal and peripapillary capillaries, causing bleeding from retinal capillaries. Another possibility is that leakage of ozone from the disc due to a microfracture of the anulus fibrosus with transient spike in cerebrospinal fluid pressure after disk infiltration could be responsible for the retinal hemorrhages.

Our considerations concerning this first case report are that the amount of 10 cc O₃O₂ injected at intradiscal level is excessive: in our experience oxygen-ozone leakage in the epidural space is common, but only a fews cc and no problem has ever arisen. The possibility of ozone leaking from the disc due to lesions of the anulus fibrosus with passage in the epidural space has also been described, but no evidence was give. This problem is not so important if the procedure is carried out under CT guidance and the cause-effect correlation cannot be proved with certainty, as the same authors declare.

In the second case report a 66-year-old woman with hypertension who had smoked 20 cigarettes/day since the age of 22 years was admitted to hospital for an abrupt onset of bilateral blindness. The patient had been admitted from a local pain clinic and had developed a tension-type frontal headache without nausea and vomiting and then almost suddenly bilateral blindness during a lumbar (L5-S1) intradiscal ozone injection for sciatica. A computed tomography scan four hours after the onset of symptoms showed multiple hemispheric subcortical lacunar lesions but no sign of recent ischemic or hemorrhagic stroke. Magnetic resonance images showed hyperintensities in the occipital cortex and frontal white matter bilaterally and in the left thalamus in the T2-weighted sequences, with diffu-
sion-weighted highlighted changes in the occipital cortex bilaterally and in the left thalamus. Magnetic resonance angiography performed within 12 hours after onset appeared normal.

The authors presented this case as similar to vertebrobasilar stroke during an oxygen-ozone therapy medical application. The invoked mechanism is that an intense painful stimulus during the procedure could have provoked paroxysmal cardiac arrhythmias leading to embolic migration of thrombotic debris from cardiac chambers. The authors specified that no radiological guidance was used during the treatment. They assume that very strong pain could be cause of arrhythmias, but if the procedure is correct patients should not suffer undue pain. Moreover it is not clear if the pain mechanism was assumed by the authors or actually referred by the patient.

Another case report described a 59-year-old woman with an unremarkable history. On hospital admission neurological examination was normal, namely muscle force, reflex responses, and the superficial sensory perception showed no changes in either leg. NCS and EMG were normal in the lower limbs. Magnetic resonance showed a posterior protrusion of the L4-L5 disk that was in contact with the proximal portion of the L5 radicular pouch and a median posterior protrusion of the L5-S1 disk with moderate bilateral foraminal stenosis. The patient was judged not to be a candidate for a conventional surgical approach. One month later she received a percutaneous intradiscal (L5) injection of an O₂O₃ mixture with an ozone concentration of 10 µg/ml. The patient did not complain of any sensation immediately after introduction of needle and drug, but a few minutes (figure 6B) after the procedure, she experienced paresthesia along the anterolateral compartment of her left leg and hypesthesia over the dorsum of the left foot. The day after, lumbosciatalgia occurred in the left limb. Subsequently a ventral and dorsal root injury was diagnosed according to clinical, physical and electrophysiologic findings.

The principal invoked mechanism is: “assuming the presence of microfractures of the annulus fibrosus, one possibility is that an abrupt, transient spike in CFP after disk infiltration was responsible for the lesions. In fact, dorsal and ventral roots, crossing through a subarachnoid space and lacking in perineurium and epineurium, are susceptible to be damaged by a sudden rise in CFP”. According to the authors, this mechanism could explain the double injury found in this patient, whereas they excluded a direct lesion by the needle because the patient did not refer any pain during the injection.

In this case we have several doubts about the procedure adopted. In our opinion the concentration used (10 µg/ml) is low and we have no information about the injection pressure. Nor do we have any elements to evaluate the technique used or whether any radiological guidance was adopted for the procedure (CT? Fluoroscopy?). In addition, we do not consider it correct to treat a bulging without radiculopathy.

The lack of information makes it impossible to understand what occurred in these adverse events published, therefore we think that they cannot be taken into consideration.

The last most recent case report of fulminating septicemia secondary to oxygen-ozone therapy failed to explain the procedure adopted correctly, and for this reason it is impossible to associate the adverse event with the therapy itself. The only thing we can understand is that the authors did not use correct asepsis and hygiene procedures. Since ozone is a very powerful disinfectant is highly improbable that this gas can create this adverse event.

**Conclusion**

When the guidelines of the Italian Oxygen-Ozone Therapy Federation are followed, intradiscal and periganglionic injection of oxygen-ozone mixture is considered safe, without any complications or collateral effects making intradiscal-intraforaminal oxygen-ozone injection under CT guidance the method of choice in the percutaneous treatment of herniated disc.

Our study covered about 12,000 patients, and all the procedures were performed following the guidelines of the Italian Oxygen-Ozone Therapy Federation (FIO) with no complications.

Hence, the low costs of oxygen-ozone therapy and the lack of any complications or collateral effects make this minimally invasive procedure safe and useful for the treatment of lumbar disc herniation, in particular in patients who have failed to respond to conservative management, before recourse to surgery or when surgery is not possible.
References


