

# Ozone therapy for lumbosciatic pain\*

## Ozonioterapia em lombociatalgia

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### SUMMARY

**BACKGROUND AND OBJECTIVES:** Most adults have several low back pain episodes during their lives. Ozone therapy is a minimally invasive method able to promote analgesia for most patients, with few reports of complications. This study aimed at reviewing the literature on the use of ozone therapy to treat low back pain and lumbosciatic pain.

**CONTENTS:** Virtual Health Library was searched using the following keywords: ozone, therapy, pain, back, lumbodynia. Search sources included: LILACS, Medline, Cochrane, Pubmed, Ibecs and scientific journals, looking for articles originally published in English, Spanish and Portuguese in recent years. Fifty-four articles were selected. Two were randomized multicenter studies, four were systematic reviews, one was a meta-analysis with more than 8 thousand patients from different centers, one was a national Italian consensus, many were double-blind studies, some had control groups and many were observational studies. The level of evidence to support a stronger recommendation is still low (II-3 for intradiscal administration and II-1 for paravertebral or intraforaminal muscular administration), however this scenario seems to be dynamic with a trend toward the indication of ozone therapy.

**CONCLUSION:** Ozone therapy was effective to treat

low back pain with or without sciatic pain, being associated to few adverse events.

**Keywords:** Low back pain, Ozone, Pain.

### RESUMO

**JUSTIFICATIVA E OBJETIVOS:** A maioria dos adultos sofre de vários episódios de lombalgia durante sua vida. A ozonioterapia é método minimamente invasivo, capaz de oferecer analgesia para a maioria dos pacientes, com raros relatos de complicações. O objetivo deste estudo foi revisar a literatura referente ao uso da ozonioterapia no tratamento de lombalgia e lombociatalgia.

**CONTEÚDO:** Realizada busca na Biblioteca Virtual em Saúde utilizando as seguintes palavras-chaves: ozone, therapy, pain, back, lumbodynia. As fontes de busca incluíram: LILACS, Medline, Cochrane, Pubmed, Ibecs, e em revistas para trabalhos, sobre estudos publicados originalmente nas línguas inglesa, espanhola e portuguesa, nos últimos anos. Foram selecionados 54 artigos. Deles dois eram estudos multicêntricos aleatórios, quatro eram revisões sistemáticas, uma era metanálise com mais de 8000 mil pacientes em múltiplos centros, um era consenso nacional italiano, vários trabalhos duplamente encobertos, alguns com grupo controle, e muitos observacionais. O grau de evidência para alicerçar uma recomendação mais vigorosa ainda é considerado baixo (II-3 para a administração intradiscal e II-1 para intramuscular paravertebral ou intraforaminal), porém, este panorama parece dinâmico e com tendência a favor da indicação da ozonioterapia.

**CONCLUSÃO:** A ozonioterapia se mostrou eficaz no tratamento da lombalgia com ou sem ciatralgia, sendo associada a poucos eventos adversos.

**Descritores:** Dor, Lombalgia, Ozônio.

### INTRODUCTION

Most adults have several low back pain episodes during

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their lives. Approximately 80% of workers miss working hours specifically due to low back pain<sup>1</sup>. Low back pain is the 5<sup>th</sup> or the 6<sup>th</sup> most common reason for people seeking for medical care. Although many times this is self-limiting, a significant number of patients need surgical treatment. Ozone therapy is a minimally invasive method able to promote analgesia for most patients, with few reports of complications.

Virtual Health Library was searched using the following keywords: ozone, therapy, pain, back, lumbodinia. Major search sources included: LILACS, Medline, Cochrane, Pubmed, Ibecs and scientific journals, looking for articles originally published in English, Spanish and Portuguese in recent years.

Fifty-four articles were selected. Two were randomized multicenter studies, four were systematic reviews, one was a meta-analysis with more than 8 thousand patients from different centers, one was a national Italian consensus, and many were double-blind studies with control groups. The level of evidence to support a stronger recommendation is still low; however this scenario seems to be dynamic with a trend toward the indication of ozone therapy.

## NOMENCLATURE

The word dorsalgia means dorsal or back pain and is made of the Latin term dorsum – posterior region of the trunk going from the neck to the pelvis, and also of the Greek word algos, which means pain. The English synonym for dorsalgia is back pain. The word lombalgia is the combination of the Latin term lumbos – which means back = part of the dorsal region between the chest and the pelvis, and of the Greek word algos – pain. In Portuguese the most common expression is low back pain being lumbodinia seldom used. The English word for lombalgia is lumbodinia being also accepted the expression low back pain. Both in English and in Portuguese there is the word lumbago, which has the same translation, although some older books suggest that this term would be better to define more caudal pains located in the transition between back and sacrum. Lumbosciatic pain means lumbar pain along the sciatic nerve and its branches, and combines the Latin terms lumbus (back) and sciatica referring to the ischium and the hip, and the Greek term algos (pain). Sciatic pain refers to pain sparing the lumbar region.

## EVALUATION OF PATIENTS SUFFERING FROM LOW BACK PAIN WITH OR WITHOUT SCIATIC PAIN

In general, history and physical evaluation separate low

back pain from sciatic pain. In the former, pain is limited to low lumbar region and buttocks and may reach the thigh. In sciatic pain, pain is irradiated to the lower limb and may reach the toes. Discomfort distribution to below the knees is highly suggestive of sciatic pain. In axial lumbar pain, the process may be predominantly mechanical or inflammatory. Inflammatory pain starts at night or during rest and is associated to morning stiffness. Mechanical pain worsens along the day and is not associated to morning stiffness.

Diagnostic investigation goes through separating mechanical low back pain, inflammatory low back pain and sciatic pain, since etiologic processes are different in each situation.

Inflammatory low back pain may, for example, be manifestation of spondyloarthritis, such as ankylosing spondylitis, reactive arthritis, spondyloarthritis of the psoriatic arthritis and of inflammatory bowel diseases. These are systemic diseases and may be followed by signs and symptoms outside the spine. They are common in young males.

Etiologic diagnosis of mechanical pain may be very difficult. Several individual factors related to local structures and the use of the spine are implied in its genesis. They are collectively called nonspecific low back pain. For these nonspecific low back pains, exhaustive search for implied etiologic elements should not be encouraged. The exceptions, less than 5%, would account for the finding of the so-called alert signal for a severe underlying disease. Chronic mechanical low back pain has preference for the elderly with previous low back pain episodes and is associated to psycho-social factors.

Pain may be axial when located proximal to the spine, and appendicular, when located in the limbs. It may be unilateral, bilateral, symmetric or asymmetric.

Projection, convergence and / or facilitation nervous system mechanisms are responsible for referred pain. Pain may be referred to the lumbar region with axial distribution when the source of original stimuli is outside the region, for example, coming from menstrual colic, urinary infection or renal lithiasis. They may also be referred from the lumbar region to the groin, myofascial syndrome of the psoas muscle, or from the lumbar region for lower limb(s), with appendicular distribution, as in lumbar facet arthropathy. Referred pain in general has imprecise limits. Anesthetic blocks of reference areas do not result in less discomfort while blocks of source structures are extremely effective.

Neuropathic pain in general generates discomfort in distal territories supplied by structures which are directly or indirectly affected. Sciatic pain is the name of the pain in the pathway and / or territory of the sciatic nerve. The

sciatic nerve is mixed and made up of fibers originating from several nervous roots and spinal nerves.

### Incidence and prevalence

Low back pain is more frequent between 35 and 45 years of age. In industrialized societies, 60% to 80% of the population will have low back pain at a certain moment of their lives. Both absenteeism from work and symptoms intensity increase with age. Half the adult population experiences one low back pain episode per year, while approximately 15% refer frequent episodes or crises lasting more than one week. The minority, 5% to 10% of adults, evolve to chronic pain.

Only 1% to 2% of patients have simultaneous low back pain and sciatic pain in crises lasting two weeks or more.

### Social cost

The prevalence of low back pain in older industrialized countries has not changed a lot in the last two decades. However, the concept of incapacity in these societies has suffered major changes, with a trend to progressively give more protection to workers. There has been increase in incapacity rate and cost, as well as in the excessive use of medical care, including surgical procedures<sup>2</sup>. In Brazil, high costs involved with the recognition of incapacity related to low back pain had already reached very high levels, even before the current situation of emergent country, due to the early development of the labor legislation since World War II, to the support of successive governments which have blended taxation policies of income redistribution, populist measures and unionist measures.

### Risk factors

As opposed to heavy physical work, those requiring low effort, less energy and of static nature, only recently were accepted as risk factor for low back pain<sup>2</sup>. Low back pain, sciatic pain, degenerative disk disease and disc hernia are associated to repetitive weight lifting, to static work posture, to frequent torsion, rotation and inclination, to varied vibrations, and to smoking, among others

### Low back pain and sciatic pain causes

Possible sources of low back pain and sciatic pain include vertebral bone structure, muscles fixed to the spine and hips, muscle fascias, ligaments, discs<sup>4</sup>, zygoapophysary facet joints, meninges, vessels, nervous roots,

dorsal root ganglia and adjacent area nerves<sup>2,5</sup>.

Lumbosciatic pain is associated to the presence of nervous compression, such as disc hernia, spinal canal stenosis, piriformis syndrome, etc. When associated to disc hernia, lumbosciatic pain worsens with Valsalva maneuver or with any other situation increasing spinal canal pressure, such as sneezing, coughing or defecating<sup>2,3,5</sup>. Spinal canal stenosis caused by zygoapophysary osteophytosis and yellow ligament hypertrophy, among others, is associated to neurogenic lameness<sup>5</sup>. Classically, patients feel pain and paresthesia while walking and improve with rest. In practice, persistent pain in legs and back is common, and it is relieved with the sitting position or trunk flexion<sup>3,6</sup>.

The piriformis syndrome is attributed to root compression by the piriformis muscle. Anesthetic infiltration may bring relief by anesthetizing the nerve itself or the muscles. Relaxation of anesthetized muscle decreases mass effect and nervous compression. Muscle stretching reinforces the effect<sup>5</sup>.

Nervous compressions may result in sciatic pain, but the mechanism goes beyond the purely mechanical aspect. This is especially true for disc hernia. The presence of immunocompetent cell response activated in the epidural interface of pulpous muscle herniation reinforces the concept of immunogenic capacity of this structure. Phlogistic response associated to disc hernia may overcome mechanical compression in the importance to generate lumbosciatic pain<sup>5,7</sup>.

### Patients' evaluation

Physical evaluation, including complete neurological evaluation, is critical for the good care of a lumbosciatic pain patient<sup>6,8</sup>. Painful paravertebral muscle hypertonia is detected by palpation<sup>6</sup>. Lasègue maneuver tests the presence of compressive mechanical involvement of the spinal root or nerve close to the spine. It consists of raising one leg with the patient lying down. If there is conflict for space, there will be pain in the tested limb, caused by the stretching of the nervous root between ten and sixty degrees. The value of the maneuver is increased when pain is relieved by knee flexion or is worsened by ankle dorsiflexion.

Crossed Lasègue test refers to the raising of the unaffected leg causing pain in the affected leg. This test may also be performed with the patient in the sitting position or standing up and slowly raising the leg. Neurological evaluation helps locating root compression which is common between vertebral levels L<sub>4</sub>-L<sub>5</sub> and L<sub>5</sub>-S<sub>1</sub>. Evaluation of muscle strength, sensitivity and myotactic and

skin reflexes may distinguish between conservative and surgical management. When motor and / or sensory deficiency is found, the possibility of irreversibility along time and even progression of the clinical presentation makes surgical indication concrete<sup>6,7</sup>.

### Subsidiary evaluations

Imaging exams or other diagnostic tests have been recommended in the last five years for patients with inflammatory low back pain or lumbosciatic pain, especially in the presence of neurological deficits or when history and physical evaluation point to underlying systemic disease. Simple X-rays do not detect disc hernia, but may catch fractures, infections and tumors, although there are false negatives. Simple X-rays have 60% sensitivity and 95% specificity for malignancies, and 82% sensitivity and 57% specificity for infections. Oblique incidences further increase the exposure to radiation, especially in females, and do not supply many other diagnostic information. Incidences in flexion and extension are useful for individuals with spondylolisthesis or submitted to fusion procedures<sup>6</sup>.

CT is better to show bone structure changes and MRI is better for soft tissue involvement.

CT seems to be particularly useful for sacroiliac abnormalities, facet arthritis, fractures, spondylolisthesis and fusions with instability, among other situations. MRI is useful to diagnose disc hernias, canal stenosis, osteomyelitis and discitis, epidural abscesses, bone metastasis, arachnoiditis, etc.<sup>6</sup>.

Myelography, once so frequent, is currently more uncommon and is indicated for selected disc injury cases and previous surgeries. Erythrocyte sedimentation rate, C-reactive protein and complete blood count may also be useful in cases of infection; protein electrophoresis in cases of multiple myeloma; alkaline phosphatase for osteoblastic metastases; in addition to tumor markers according to the organ suspicious of giving origin to the painful process<sup>6,7</sup>.

All image findings should be carefully interpreted in close association with clinical findings. In spite of republicans and democrats, clinic is still sovereign. People are operated on, not their exams.

### Non interventionist management

Provided sensory-motor deficiencies are not detected, lumbosciatic pain management is preferably conservative. Even for disc hernia, there is great possibility of, with time, vertebral canal remodeling, progressive dehy-

dration of herniated material, decrease not only of compression but also of the involved phlogistic presentation. Initially, when pain is acute, management may include a brief resting period<sup>9</sup> and common analgesics. Muscle stretching and trunk strengthening exercises may be implemented very carefully and be limited by patients' pain. Drug therapy, in addition to attempting to promote analgesia, helps rehabilitation, restores sleep, mood and motivation patterns. Non-steroid anti-inflammatory drugs are especially indicated for inflammation; however their prolonged use should not be encouraged. Older, low cost tricyclic antidepressant drugs, however more toxic than more recent high cost and less toxic dual drugs, are extremely useful for neuropathic and myofascial pain, and for chronic cases.

Prescription alone is not enough and should be followed by didactic actions by the team assisting the patient. Convincing, critical for patients' adherence, is achieved by explaining the reasons leading to the indication of drugs originally indicated for other situations, especially those against seizures, depression and other neuropsychiatric disorders.

Red tape and financial obstacles lead to inadequate update of package inserts and many indications become obsolete. Not labeled or not endorsed insert indications are more updated and better justified than those present. Several countries adopt inserts with minimalist information, while in others, such as Brazil, true monographies contribute to create a lay, extemporaneous and noxious culture which invariably impairs the adhesion to prescribed treatment and sometimes may induce self-medication.

Neuromuscular blockers help decreasing spasms and improve sleep. Opioid analgesics are important to promote a restoring rest and to maintain activity during acute lumbosciatic pain phase. Prolonged use of both drugs should be discouraged for most patients and should be reserved just for those carefully selected.

After approximately one and a half month, if discomfort persists and no underlying condition is detected, immobilization should be strongly discouraged<sup>6,9</sup>. Physical therapy is indicated and movement is encouraged. Body weight control and posture correction may be beneficial. Vertebral manipulation is contraindicated in cases of lumbosciatic pain or in conditions caused by radiculopathies, or even when there is no diagnosis.

### Minimally invasive or interventionist management

Traditional minimally invasive interventionist management contemplates drug injections, in general local anesthetics and / or steroids in trigger points; traditional in-

terlaminar epidural injection of steroids; transforaminal or perineural epidural injection of steroids; intra-articular block of the zygoapophysary joint or medial branch blockade. Currently, interlaminar injection of non particulate steroids is recommended for the lumbar region due to lower chance of embolic complications.

Modern minimally invasive interventionist management added to the armamentarium against low back and sciatic pain includes epidural neuroplasty or epidural adhesiolysis, which associates saline solution to hyaluronidase; ozone therapy, adopted in Brazil only for scientific research purposes; epiduroscopy, described with simultaneous use of ozone therapy; denervation of zygoapophysary facets by percutaneous radiofrequency of medial branches; chemonucleolysis, using chymopapain as vehicle is not being used, may be complicated by anaphylaxis, meningeal hemorrhage, infection and transverse myelitis; automated percutaneous discectomy using alternate cut and aspiration device; laser percutaneous disc decompression using ablation or partial vaporization of the nucleus pulposus; intradiscal electrothermal therapy, also called annuloplasty, denervates and remodels the disc decreasing its internal pressure and innervation; percutaneous intradiscal nucleotomy with nucleoplasty for discogenic pain of contained disc; percutaneous lumbar discectomy with probe for discogenic pain of contained disc, spinal neurostimulation especially useful for appendicular, neuropathic and stable pain, which does not predominantly depend on external stimulations, such as radiculopathies following sequelae; intrathecal administration of drugs, reserved for few selected patients; percutaneous vertebroplasty, which decreases the use of analgesics and bed rest and hospitalization time; and percutaneous kyphoplasty, indication similar to vertebroplasty and associated to lower risk of complications.

## OZONE THERAPY

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, Prussian, patriarch and founder of the industrial conglomerate named after him till today.

Ozone is in fact, a mixture of ozone and oxygen ( $O_3/O_2$ ) where ozone is no more than 5% of total mixture. One of the best known ozone action is germicide<sup>10,11</sup>. The effect on water sterilization is internationally accepted. Lack of residues characterizes ozone treatment as preferential to produce drinking water. Several water

treatment stations with ozone are spread worldwide.

Ozone to treat infections is documented since the 19<sup>th</sup> Century. Topic, subcutaneous, muscular, venous or rectal ozone acts against bacteria and fungi which do not have protection systems against oxidative aggression<sup>11</sup>. Application routes may trigger local, regional and / or systemic effects. Topic, subcutaneous, intra-articular and muscular routes trigger predominantly local and regional effects, while venous and rectal routes trigger predominantly systemic effects. Therapeutic responses of ozone therapy for infections transcend exclusively local or regional responses<sup>10-12</sup>.

Topic route may be used with the simple exposure of the target-area greased or moistened with water, saline solution or pre-ozone oil, with or without suction systems coupling. The other routes are used by injection or inflation of the gaseous mixture  $O_3/O_2$  or through ozonized blood.

Muscle pains of different etiologies, especially those related to lactic acid build up and subsequent decrease of local pH, are relieved with  $O_3$ .

Intra-articular injection brings major decrease of phlogistic phenomena and marked functional improvement of traumatic, infectious and degenerative arthralgias<sup>13</sup>. Joints with more isolated or compartmented anatomy, such as knee and interphalangeal joints are those with best analgesic effects.

Spinal pains, such as cervical pain<sup>14,15</sup> and low back pain (with or without sciatic pain) are treated with intradiscal, regional subcutaneous, paravertebral supralaminar muscular and rectal inflation ozone therapy, and by muscle or venous self-hemotherapy<sup>12,16</sup>. Management may combine different administration routes.

Richer ozone concentrations, which for medical use do not go beyond 5%, 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  $\mu$  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<sup>1,4,17,18</sup>.

## Ozone therapy mode of action

Oxidation is the capacity of a substance, in a chemical reaction, to donate one electron to the other substance. Examples of oxidative substances are: vitamin C, hydrogen peroxide, potassium permanganate and ozone.

Oxidative or bio-oxidative therapies use the ability of substances to oxidize others to promote some type of therapeutic benefit. Ozone therapy is one of the existing oxidative therapies.

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.

Antioxidant systems may be enzymatic and non enzymatic. Enzymatic systems include actions of superoxide dismutases, catalases, peroxidases of glutathione and glutathione redox system. Non enzymatic systems may be water-soluble or lipid-soluble or even a subgroup of kelating proteins. Water-soluble systems include the actions of uric acid, ascorbic acid, glucose, cysteine, cysteamine, taurine, tryptophan, histidine, methionine, plasma proteins and growth hormone release stimulating factor. Lipid-soluble systems conceive the actions of vitamin E, vitamin A, carotenoids, coenzyme Q, alpha-lipoic acid, bilirubin, bioflavonoids, tioredoxin and melatonin. Kelating proteins include actions of transferrin, ferritin, ceruloplasmin, lactoferrin, hemopexin and albumin<sup>12,19</sup>.

Ozone is rapidly inactivated and, depending on the buffering system, results in the formation of the so-called ozonides, reactive species of oxygen or of lipid oxidation products<sup>12,19,20</sup>.

Oxygen reactive species are potentially cytotoxic, however the very short half life of these substances, with the exception of the semiquinone radical and hypochlorous acid, decrease the risk of cytotoxicity, provided applications follow strict selection of patients and doses for each mode of application recommended by national and international protocols of medical ozone therapy associations. Lipid oxidation products are heterogeneous and are represented by peroxy and hydroperoxide radicals and by a complex mixture of low molecular weight aldehydes and alkenes. They reach the vascular system and may signal responses in almost all the body. Toxicity of these substances is lower than those produced in hydrous mean. Half life of lipid ozonides is longer than that of hydrous ozonides<sup>12</sup>.

Hydrous ozonides increase erythrocytes flexibility, perform leukocyte immunoactivation and cause autacoids degranulation and growth factors by platelets. Lipid ozonides increase the enzymatic action of nitric oxide synthetase and, as a consequence, the endothelial supply of this gas; they induce myeloproliferation of more lon-

gevous erythrocytes with higher capacity of transporting and releasing oxygen to peripheral tissues; and diffusely regulate the antioxidant system<sup>12,21</sup>.

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. O<sub>3</sub> increases 2,3DPG concentration with decreased affinity of oxyhemoglobin for O<sub>2</sub> and a shift to the left in the HbO<sub>2</sub>/Hb curve with consequent better peripheral oxygenation<sup>12,21,22</sup>.

Peroxidation reaction on phospholipids of erythrocytes membrane determines increase in their negative electric charge causing electrical repulsion which leads to a disaggregation phenomenon of decreased cell adhesion, inactivating fibronectins, integrins and other adhesion molecules. Erythrocytes piling process is extremely decreased inhibiting the formation of red clots<sup>12,21,22</sup>. Induced change in red blood cells gives them higher deformation and gas exchange capacity. Decreased blood viscosity is another consequence of ozone. Similar effects are obtained with platelets, giving to ozone therapy also an anti-adhesive and prophylactic effect against white clots<sup>21,22</sup>.

So, ozone therapy optimizes hemoreological parameters and the ability to release oxygen to tissues in patients with ischemic diseases<sup>21,22</sup>. Supply and build up of tissue energy are markedly increased, translated by ATP concentration increase. This higher supply, and subsequent energy build up, seems to be closely related to the attenuating effects of signs and symptoms of fatigue and muscle pain. Direct ozone antimicrobial action against bacteria, viruses and fungi is powerful<sup>10,11</sup>. These microorganisms lack antioxidant buffering systems and the stress caused by O<sub>3</sub> cannot be controlled, making them fragile<sup>11</sup>. Ozone therapy does not supply ozone or ozonides in sufficient amounts to directly act against microorganisms<sup>12</sup>. Distant microbicide effects are due to metabolic changes signaled and triggered by ozonides, and to ozone production, such as biomolecule, by activated neutrophils and catalised by specific antibodies<sup>10,11</sup>.

Leukocytes attack infectious agents through ozone and / or molecules with similar properties, such as peroxides<sup>10</sup>. Short chain hydroperoxides enter cell nucleus and culminate with messenger RNA activation, translation, consequent protein production and cytokines release. The activation of immunocompetent cells with cytokines induction, such as interferons, interleukins and growth factors, signaling molecules, modulates the immune system<sup>12</sup>.

Ozone therapy-induced changes in blood rheological characteristics, added to mean responses and microcirculations have provided the possibility of managing and relieving several affections involved with ischemic dis-

orders, associated or not to infectious complications<sup>21,22</sup>. Several amputations were and may be avoided in the future with ozone therapy<sup>21,22</sup>.

Antioxidant response which follows controlled oxidizing stimulation supplied by medical ozone is represented by the increase of substances classically known as anti-inflammatory and already described. Most analgesic effects come from this response.

ost pains mediated by increased muscle activity are relieved by ozone therapy. 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<sup>19,20,23,24</sup>.

When combined with steroid injection, ozone therapy has anti-inflammatory synergism which occurs in different times<sup>25-28</sup>.

Subcutaneous inflation of ozone and oxygen mixture in mice has prevented allodynia and has decreased the exaggerated expression of pro-inflammatory enzymes from the caspases family in orbito-frontal cortex parenchyma of rodents with neuropathic pain models<sup>29</sup>. Response found may suggest that ozone therapy protects some cells from apoptosis.

When used as conditioning after injury caused by disc hernia compression and inflammation in humans, ozone therapy has decreased oxidative injury proteins concentration<sup>24</sup>.

### **Surgical management of lumbar pain with or without appendicular pain**

Surgery should be considered in the lack of response to conservative treatment. Surgical indications include: severe and incapacitating pain, pain persistence or worsening after conservative attempts for more than four weeks and, especially, presence of root dysfunction, motor or sensory deficiency and correspondence with imaging results showing root compression.

Several surgeries may be indicated to manage lumbosciatic pain and include laminectomy, macro or micro discectomy, foraminotomy, spinal arthrodesis and fusion, and artificial prosthesis implant, among others<sup>5</sup>.

Procedures aim at decreasing movements, decompressing nervous structures, especially roots, and at promoting conditions for regeneration and reduction of the local phlogistic phenomenon.

### **Results about the efficacy of the mixture O<sub>2</sub> / O<sub>3</sub>**

Ozone therapy is an intraoperative method to prevent in-

fections, but it still lacks adequately documented scientific evidences<sup>30</sup>. Some papers report pain improvements with the use of methods such as epiduroscopy, however they do not value the simultaneous use of ozone therapy<sup>28,31</sup>. Not even partial credits, in some articles, are given with emphasis. The non recognition and, consequently, the lack of routine approval (with exception of scientific research) of this therapy by health surveillance agencies in some countries may be responsible for the contempt of ozone therapy analgesic actions.

In almost all articles found, ozone therapy was effective to manage low back pain with or without sciatic pain<sup>16,32-34</sup>. Observational papers, invariably, have revealed positive results to control pain both in short and long term follow up periods<sup>35-46</sup>.

A recent meta-analysis has included 12 articles with more than 8 thousand lumbosciatic or low back pain patients and has shown no differences in painful discomfort and function between patients who were operated on and those treated with ozone therapy; however the group treated with O<sub>3</sub>/O<sub>2</sub> has evolved with lower complication rates and shorter recovery period<sup>33</sup>.

Another randomized and double-blind study has shown that when combined with already accepted strategies to relief lumbosciatic pain secondary to disc hernia, such as local anesthetic and steroids infiltration, the group also receiving ozone therapy had better pain control because success rate went from 47% to 74%<sup>25</sup>.

Recent randomized double-blind study has compared the results of intraforaminal or periradicular infiltrations with steroids in a group and of oxygen / ozone mixture infiltration in other. Participated in this study 306 low back pain patients with or without appendicular discomfort due to discal and non discal vertebral disorders. At the end of six months, the group treated with the ozone and oxygen mixture had higher return to work rates and was pain free<sup>47</sup>.

In 2009, a multicenter, randomized and double-blind study has compared a group of 36 patients with lumbosciatic pain due to lumbar disc hernia treated with paravertebral injection of ozone and oxygen mixture, to a group of 24 patients with the same disease and treated with subcutaneous injection of knowingly inactive substances. Among patients of the first group receiving ozone therapy, 62% were pain free and only 5% of them needed surgical management to remove the hernia, as opposed to the other group where only 33% were pain free and 16.7% needed surgery<sup>48</sup>.

Few complications included vertebrobasilar stroke<sup>49</sup>, infections<sup>50,51</sup>, vitreoretinal bleeding<sup>52</sup>, thunderclap headache related to subarachnoid injection and pneumocephala-

lus formation<sup>53</sup>, dysesthesia and hypoesthesia related to possible root involvement during discal puncture<sup>54</sup>, and subcutaneous hematoma, among few others. The method is considered effective and very safe<sup>55</sup>, even when applied to the elderly<sup>40</sup>. To treat patients with lumbar disc hernia, ozone therapy was safe in terms of neurological evolution not being related to higher sequelae rates; on the contrary, decompression surgeries became less frequent<sup>48</sup>.

A systematic review and meta-analysis about ozone therapy for lumbago secondary to disc hernia, published in 2012, has indicated evidence level II.3 based on at least one well-designed paper, however with low diagnostic precision for the intradiscal administration, and II-1 based on at least one well designed scientific paper and with good sample size for paravertebral muscular, supralaminar or periforaminal administrations<sup>8</sup>.

Current recommendation based on scientific evidences is strong: level 1.C – strongly recommended, waiting for future evidences of better quality for intradiscal administration and 1.B – strongly recommended based on evidence of at least moderate quality for intramuscular, paravertebral or periforaminal administration<sup>8</sup>.

There is a worldwide Herculean effort in the search for safer and less invasive treatments to relieve low back pain and lumbosciatic pain. Given the increasing build up of favorable international scientific production, ozone therapy, which in our country is only allowed for scientific research, deserves reevaluation on the part of our Regional Councils of Medicine. Patients with axial low back pain with or without appendicular root or referred involvement, in the lack of neurological evidences, may benefit from this method.

## CONCLUSION

Ozone therapy was effective to treat low back pain, with or without sciatic pain, being associated to few adverse events.

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- Submitted in February 14, 2012.  
Accepted for publication in August 02, 2012.