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Indexed in: EMBASE, Elsevier
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Programma preliminare

Giovedì 28 Maggio
h 18.00 Cerimonia d’apertura del Congresso

Venerdì 29 Maggio
h 09.00-10.30 Workshop tematici in video conferenza
  ❍ Infiltrazioni TAC guidate
  ❍ Infiltrazioni articolari
  ❍ Infiltrazioni paravertebrali
  ❍ Grande e Piccola auto emo terapia
h 10.30-11.00 Lezione Magistrale “Attualità in tema di Ossigeno Ozonoterapia”
  Presidente W.F.O.O.T.: V. Kumar
h 11.00-11.15 Coffee break
h 11.15-12.45 I Sessione “Ossigeno Ozonoterapia nelle ernie e protrusioni discali”
  ❍ Infiltrazioni TAC guidate
  ❍ Infiltrazioni paravertebrali
  ❍ Discussione h 12.45–13.15
h 13.15-14.15 Colazione di lavoro
h 14.30-17.15 II Sessione “Infiltrazioni articolari”
  ❍ Discussione h 17.15–17.30
h 17.30-17.45 Coffee break
h 17.45-18.30 III Sessione “Attualità in tema di GAET”
  ❍ Discussione h 18.30–18.45
h 18.45-19.30 IV Sessione “Miscellanea”
  ❍ Discussione h 19.30–19.45

Sabato 30 Maggio
h 9.00-12.00 SIMPOSIO SATELLITE
  Medicina Estetica,
  Ossigeno Ozonoterapia,
  Omotossicologia
Editorial

FIO – Italian Federation of Oxygen-Ozone Therapy
National Congress 2007

F. DE SANTIS

Department of Neuroradiology, Bellaria Hospital; Bologna, Italy

The National Congress of the Italian Federation of Oxygen-Ozone Therapy was held in Bologna on 12th and 13th October 2007. Since its first edition this annual event has been attracting growing interest in the new field of ozone therapy. So much so that the large number of scientific papers received and the growing demand for theoretical-practical work sessions meant that the latest meeting had to be scheduled on two days rather than one.

The first day of the Congress was devoted to theoretical-practical work sessions aimed at physicians eager to learn about ozone treatment by seeing in vivo application of the different techniques by expert operators giving guided explanations. Four different workshops were run in parallel in different rooms and focused on intradiscal (cervical and lumbar) ozone therapy, paravertebral intramuscular ozone therapy, intra and peri-articular ozone therapy, and oxygen-ozone autohaemotransfusion.

Enthusiastic participants responded to this schedule by “invading” the Neuroradiology Unit run by Prof. Leonardi to whom we offer our sincere thanks for his lively teaching during the workshops and his help with the organization of the entire Congress. The second day of the meeting focused on oral presentations covering myriad applications of ozone therapy from the more well-established treatments to ongoing new developments.

Prof. Bocci, the leading expert on ozone therapy, warned against any excess enthusiasm with the new treatment. His lecture outlined the qualities and defects of ozone, highlighting the basic tenets to bear in mind to enhance the benefits and safety of ozone treatment.

Lack of space prevents me citing each of the speakers by name for their commitment and enthusiasm, but I would particularly like to mention one study reporting the successful results obtained by doctors Izzo and Bertolotti in treating Buruli ulcer at “La Croix” hospital run by Camillian monks in Zinvié, Benin. Without wishing to sound rhetorical, I cite this work not because it was better than others, but because I truly believe that for its followers ozone therapy arouses not only enthusiasm over its efficacy, but also satisfaction and joy at the benefits this low cost treatment can bring to patients with a highly debilitating disease living in disadvantaged areas.

In addition to the FIO National Congress, further evidence of the healthy status of oxygen-ozone therapy came from the important results obtained in the international arena by the WFOOT thanks to the tireless work of its members, first and foremost its Chairman Prof. V. Kumar. Other successes include the World Congress of the WFOOT held in Beijing in September 2007, the Syrian Ozone Therapy Congress held in Damascus in May 2007, the recognition of oxygen-ozone therapy in Australia and the invitation from the Russian Society of Neurosurgery extended to Prof. Leonardi, Dr Andreula and Dr Bonetti to be speakers on oxygen-ozone therapy at its next National Congress. These and many other milestones show that oxygen-ozone therapy has a long and promising future. With this conviction I send greetings to all fellow members of the WFOOT and all my ozone therapist colleagues, particularly those who attended the Congress, inviting them to support our scientific activity in forthcoming meetings and in our journal.
Bando di concorso per l’ammissione al
CORSO DI FORMAZIONE PERMANENTE
“IL TRATTAMENTO PERCUTANEO DELL’ERNIA DISCALE
CON OSSIGENO-OZONO TERAPIA”

Sede di BOLOGNA
Anno Accademico 2007/08
Scadenza Bando: 15 Maggio 2008
Il Corso si effettuerà il 31 Maggio 2008

L’Alma Mater Studiorum - Università di Bologna, sede di Bologna, ai sensi del Decreto 22 ottobre 2004, n. 270 del
Ministero dell’Istruzione dell’Università e della Ricerca, attiva, per l’anno accademico 2007/08, il Corso di Formazione
permanente in “Il Trattamento Percutaneo dell’Ernia Discale con Ossigeno-Ozono Terapia”.
In particolare il corso si rivolge a: Neuroradiologi, Specialisti e Specializzandi in Radiologia.
Ulteriori informazioni su obiettivi, scenario professionale e programma didattico sono illustrati nella scheda di presentazione
del corso pubblicata sul sito: http://www.unibo.it/Portale/Offerta+formativa/AltaFormazione/default.htm.
Al termine del corso sarà rilasciato un attestato di partecipazione condizionato alla frequenza del 70% delle ore totali del
corso. Il corso è attivato con il supporto amministrativo ed organizzativo di Fondazione Alma Mater e di Dipartimento di
Scienze Neurologiche.

Lezioni del Corso: L’ERNIA DEL DISCO CERVICALE E LOMBARE
LA CLINICA
INDICAZIONI AL TRATTAMENTO PERCUTANEO INTRADISCALE
MECCANISMO D’AZIONE DELL’OZONO
TECNICA DI IMPiego
RISULTATI, CASISTICA PERSONALE
IL CONSENSO INFORMATO

Contributo totale al Corso: La quota di iscrizione è pari a complessivi euro 300,00 da pagare in un’unica rata all’atto
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ore 11,15 - martedì e giovedì dalle ore 14,30 alle ore 15,30.
In caso di spedizione il recapito postale è invece il seguente: “Alma Mater Studiorum - Università di Bologna, Settore Post
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Si avvisa che gli unici mezzi di pubblicità, oltre al presente bando di concorso, sono le comunicazioni e le informative
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aggiornamenti apportati alla pagina: http://www.unibo.it/Portale/AltaFormazione/default.htm.
Is Medical Ozone Safe when Injected Intra-articularly?
A Comparative Histological Study in Rat

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Key words: ozone, safety, cartilage

SUMMARY - The therapeutic use of ozone (O₂-O₃) gas is controversial. Some authors claim the gas mixture is toxic and therefore out of the question, whereas, others hold that it is useful and effective when used following a certain method to treat degenerative diseases, such as knee osteoarthritis, for which the gas has been used empirically. The present work studied the effects of contact of O₂-O₃ with healthy knee tissues of Wistar rats and compared them to intra-articular injection of a substance known to damage the cartilage. Thirty-six Wistar rats were studied in two groups. Mono-iodoacetic acid (MIA) was injected in the first group in a single dose, whereas O₂-O₃ was injected in the second group in frequent doses three times a week for three weeks. The rats were killed 40 days later and articular cartilage and surrounding tissues were studied histologically. MIA caused degenerative osteoarthritis gradually deteriorating at the knees of the first group whereas no major changes were observed in those of the second group. We conclude that following the methodology of our study medical ozone appears to be safe for use.

Introduction

Knee osteoarthritis (OA) is a common high cost disease in orthopaedics and decreases the quality of life especially in the elderly. The main characteristic of OA is degeneration of the articular cartilage and the subchondral bone frequently followed by inflammation of the synovial membrane and aggravation of the supporting structure of the knee. The result of all these is pain and dysfunction in the mobility of the knee. Total joint replacement usually constitutes the final suggestion for the rehabilitation of these patients, but it is not free of complications. Thus, when applying this treatment, side-effects, age, weight and general physical condition of the patient must be taken into consideration.

Conservative treatment constitutes the first choice and many proposals have been made to alleviate symptoms, expecting at the same time an improvement in the histological features. The usual pharmacological recommendation includes analgesics, non steroidal anti-inflammatory drugs, diacerein, chondroitin sulphate, glucosamine sulphate, magnesium and others. Intra-articular injections also constitute a frequent choice and the injection of corticosteroids in acute pain or hyaluronic acid (when we also seek to improve damage to the cartilage) and have been applied for many years.

Biochemical changes in the levels C6S, C4S, and KS, TN-C² chemokine, endothelin and transforming growth factor alpha³ metalloproteinases (MMP), cytokines such as IL-1 and TNF - alpha⁴ and others appear to influence the development of osteoarthritis.

For some years intra-articular injection of medical ozone (O₂-O₃) has been suggested for the treatment of knee osteoarthritis symptoms and positive results have been reported⁵. However, its application appears to be empirical and no histological or biochemical studies have provided evidence for the repercussions of its use.

Ozone’s powerful oxidant factor⁶ has been reported to be toxic⁷,⁸,⁹,¹⁰ and hence there is scepticism concerning its use for medical purposes. Other studies have shown that if ozone is used rationally it is safe¹¹ and therapeutic for certain diseases. Medical ozone (O₂-O₃ mix) appears to behave as a bioregulator¹² when it comes into contact with a biological liquid, releasing factors from human endothelial cells¹³ and normalizing the cellular redox balance¹⁴,¹⁵. Studies have shown
its capacity to alter the levels the cytokines 16 such as TNF-alpha 17, IL 18 and platelet-derived growth factor (PDGF), transforming growth factor beta1 (TGF-beta1), interleukin-8 (IL-8) and other 19,20 indications of a likely effect of this gas on the articular cartilage when it is injected intra-articularly. Provided that ozone is indicated for use as a therapeutic means, due to its well-known antiseptic property 21,22 23,24, it would also succeed in reducing the potential dangers of septic arthritis after intra-articular injection of the gas mixture.

Controlled degeneration of the articular cartilage for experimental purposes can be caused by mechanical techniques 25 or by injection of chemical substances into the knee joints 26. Monoiodoacetic acid (MIA) is a material that could cause osteoarthritis in the knees of Wistar rats similar to those of humans 27,28. Rodents are the most widely employed species for these studies, because their night and day activity has been studied extensively and several models of osteoarthritis were developed using mice, hamsters and Wistars. The present study constitutes the first stage of comparison of histological changes and recommended methodology for the proof of action of intra-articular injection of O₂-O₃ mix and MIA in knee tissues.

Figure 1  Sacrifice at 10 days. Initial degeneration of the cartilage with modification of the natural tissue to fibrosis, hyperaemia of the subchondral bone. H.E.×45.

Figure 2  Sacrifice at 40 days. Total destruction of the architecture of the articular cartilage. H.E.×45.
Material and Method

Thirty-six (36) male wistar rats weighing 150-180g were employed in our study. A variable volume (5 to 50 µL) automatic pipette was required. An ozone generator (Multiossigen mod. PM 93, Italy). Biochemical reactors (Iodoacetic acid I 8136 amp 5×500 mg, Sigma-Aldrich). The animals were divided into two groups. After anesthesia and disinfection a pre-set quantity was administered intra-articularly:

1. First group (18 Wistars): MIA was injected into the posterior joint of the right knee while the posterior joint of the left knee (placebo) was injected with NaCl solution.

2. Second group (18 Wistars): O₃-O₂ mix was injected into the posterior joint of the right knee while in the left knee joint (placebo) was injected with O₂.

The animals remained in plastic cages throughout the experiment. They were exposed to light every twelve hours (6-18) and the temperature was maintained at 20°C. The subjects received a short anesthesia with the use of ether, long enough for the action, and after the treatment they were returned to their cages. The rats were killed by ether overdose.

Figure 3 Normal articular cartilage (water, collagen and proteoglycans the surface layer thicker than the deeper layers). Tissue sections of the normal articular surface where the cells of the main membrane of histocell fibroblasts fat cells and mast cells are evident.

Figure 4 The tissues in and around the knee (apart from the cartilage) did not show any major alterations in the long run.
The Wistars in the first group (MIA) were killed at two different times. Nine (9) rats ten days later, and nine rats 40 days later. The quantity of MIA had been set at 0.3 mg (corresponding to 0.05 ml of substance) per knee.

For the Wistars in the second group (O₂-O₃ mix) the O₂ and the O₂-O₃ mix injections were made three times a week for nine sessions in total. The administered quantity had been set at 0.05 ml in concentrations of 20 µg O₃/ml O₂ concentration empirically used for the treatment of osteoarthritis in humans.

The cartilage samples and the synovial membrane were studied histologically after being put in test tubes containing formalin 1/10.

**Results**

**MIA**

A) Macroscopically, the tissues in and around the knee (except for the cartilage) did not show major alterations.

B) Macroscopically and microscopically, the articular cartilage presented considerable degenera-
tive alterations which gradually worsened in two phases with characteristics of non-specific arthritis (figures 1 and 2).
C) Knee joints infused with 0.9% NaCl (placebo) (figure 3).
D) During the study there were no side effects or animal losses except for the reduction of the mobility of the right knee in the animals of the first group (MIA).

\[ O_2-O_3 \]

A) During the histological testing, no significant change occurred in the cartilage or synovial membrane of the healthy knee animals, either after ozone administration (figures 4 and 5) at the pre-defined concentration for our experiment, or after the oxygen (figure 6).
B) No undesired event or animal loss.
C) On the contrary, a shorter recovery period was observed after the anesthesia and an increased mobility of the animals.

Discussion

Ozone in the form of an \[ O_2-O_3 \] gas mix has been recommended for many years as a treatment for many diseases.\(^{23,29,30}\) Initially, its application was limited to the positive nutritional effects on tissues due to the improvement the gas induces on the circulation.\(^{32,33,34,35,36,37,38,39,40}\) Today, the knowledge and wide use of medical ozone as a treatment in the form of major AHT and/or AHTs constitutes a challenging, safe and effective method if applied properly.\(^{23,29}\) Today's widest use of \[ O_2-O_3 \] is mainly with the treatment of herniated disc and its symptoms. Its administration in the form of a gas mixture is direct (intradiscal or intraforaminal) or indirect by intramuscular injection into the paravertebral muscles.\(^{41}\)

Ozone is a disputed gas. According to some authors, it is a powerful oxidant harmful to the human body. Skepticism concerning its administration and doubts over its therapeutic indications in any of its forms constituted a conviction for a considerable number of doctors. Ozone application, which was a personal choice of the consulting physician. Although the gas was administered empirically, physicians ascertained daily remarkable therapeutic results, absence of side-effects and their patients' appreciation for their method. Its acknowledgement and acceptance in the broader medical discipline has changed since Bocci's research became known and a set of rules and conditions under which \[ O_3 \] once considered potentially toxic, can be therapeutically useful, was introduced. Today we know why and how the result is achieved in a series of diseases and how this low-cost and manageable element can be used.

Studies on orthopaedic diseases are mentioned in clinical findings, dealing mainly with disc herniation. The satisfactory outcome has been ascribed to the activation of the immunogenic system by the ozone, which has an anti-inflamatory action due to lipid peroxidation products with a consequent inhibition of cyclooxygenase-2.\(^{44,45}\)

A crucial factor, which accompanied the monitoring of results, was the strengthened constancy of the studied gas with the construction of ozone generators which continuously monitor the concentration of ozone in real time by a photometer calibrating system.

An initial histological and biochemical study examined: a) histologically, discs from patients operated while treated with \[ O_2-O_3 \] and b) histo- and bio-chemically, discs and their soft tissues on animals (rabbits) after intradiscal or paravertebral infusion. Findings showed the close connection between ozone concentration in the circulation and the levels of cytokines (IL, IF, TNF)\(^{46,47}\). Ozone concentration within the \[ O_2-O_3 \] mixture injected is the most crucial factor because it is what controls the movement of blood vessels and other elements of the blood. The concentration and quantity of \[ O_2-O_3 \] chosen in this study was the one which has long been used empirically, adjusted to the weight of the animal.

This is the first of a series of studies designed to show whether the medical ozone, empirically used for the treatment of knee osteoarthritis, is experimentally safe, and whether it promotes the re-establishment of the damaged cartilage. The methodology followed was the same for both groups, with the only modification being the route of administration. Multiple infusions of medical ozone were chosen (three times a week for three weeks) so that the results will go to extremes, if they are destructive. The \[ O_2-O_3 \] concentration selected was the one which has been used empirically by man for patients suffering from knee osteoarthritis: 20 µg \[ O_3 \]/ml \[ O_2 \]. The schedule of the histological and clinical effects is also described in this study. Based on this data concerning the animals (Wistar rats their general clinical condition before, during and after MIA and \[ O_2-O_3 \] infusion was simultaneously monitored. Special emphasis was placed to the mobility of the knees front and rear (treatable). It was deemed possible that for a further comparison to demonstrate the heterosid- ed knee of the study 0.9% NaCl be administered for the MIA and \[ O_3 \] for the \[ O_2-O_3 \].

The histological samples were \[ O_2-O_3 \] by a specialized histopathologist and the Mankin\(^{46,47}\) (table
The intra-articular infusion of O₂-O₃ did not cause apparent changes in the mobility of the knees and has not caused histological damage to the articular cartilage or the synovial membrane (tables 2 and 3). The clinical condition that mainly concern the mobility of the studied knees is comparable to the one where the knees were infused with pure oxygen or saline solution. Monoiodoacetic acid (MIA) and the degenerative findings it caused proved the correctness (tables 4-7) of the employed technique and the fact that it always constitutes a sufficient method for causing experimental osteoarthritis and comparison of therapeutic material when needed. All the materials used were bearable for all the animals judged from the observation of the behaviour of our samples (fatality, aggressiveness, claudication, cordial disorder).

The animals whose knees were infused with O₂-O₃ recovered faster after the completion of the treatment. This is possibly due to the development of some kind of metabolic acceleration mechanism of the narcotic substance (ether) or directly due to oxygen-ozone which could have entered the circulation during the filtering through the synovial membrane.

The increase in life expectancy means a greater frequency of knee osteoarthritis of the elderly which in conjunction with negative working practices that cause cartilage disorders even at younger ages make new methods for the treatment and alleviation of the symptoms even more imperative. Medical ozone is already used empirically by many physicians as a supplementary or single therapy. If the histological results confirm these findings this will give a crucial boost to this method for treatment knee disease.

Leaving aside the ozone production machine, the cost of the materials and the gas mix is mini-

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<td>5</td>
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<td>Complete disorganization</td>
<td>6</td>
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<tr>
<td>II. Cells</td>
<td></td>
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<td>IV. Tidemark integrity</td>
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<tr>
<td>Crossed by blood vessels</td>
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Table 1: Histological and histochemical grading system for evaluation of articular cartilage degeneration (Mankin et Al).

<table>
<thead>
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<tbody>
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<tr>
<td>Dx18</td>
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Table 2:
mal. The already extensive bibliography on ozone behaviour in the body and especially in the immune system and herniated disc, and its local antiseptic activity, gave a starting point and provided scientific grounds for this therapeutic method.

It is imperative that this be proven experimentally before any extensive use. The present study shows us that there was no histological damage and the next study will investigate the therapeutic properties of $O_2-O_3$. 

### Table 3

<table>
<thead>
<tr>
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### Table 5

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### Table 6

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### Table 7

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Conclusion

This research shows that the intra-articular infusion of MIA caused osteoarthritis in the animals very soon after injection. This step is considered necessary for the study of treatment techniques for knee maintenance or operation, initially on animals and later on humans. The intra-articular infusion of medical ozone to the healthy tissues of the knees of Wistar rats does not cause local damage or any undesired systematic or local events. On the contrary, the shorter recovery period after the anesthesia and more rigorous activity of the Wistars was observed compared to the rats treated with MIA. These findings could constitute the grounds for a study of pathological knees and the first step towards the dictum “primum non nocere” for a potential therapeutic method.

References


Ozone Injection Therapy for Lumbar Facet Joint Syndrome

A Prospective Study

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Neuroradiology Service, City of Brescia Clinical Institute; Brescia, Italy
* Chair of Radiology, University of Florence; Florence, Italy

Key words: facet joint infiltration, lumbar infiltrations, oxygen-ozone, medical ozone, low back pain

SUMMARY - Lumbar facet joint syndrome is a common condition affecting around 80% of patients with low back pain. This study aimed to assess the therapeutic efficacy of CT-guided oxygen-ozone infiltration of the lumbar facet joints. We selected 58 patients presenting pain caused by the facet joint syndrome resistant to physical and pharmacological treatment. After O₃ injection 38 (65.5%) patients had a complete remission of pain immediately after treatment. At clinical follow-up using a modified McNab method the percentage success rate had dropped to 55.1% (32/58) one month after therapy, 46.5% (27/58) after three months and 36.2% (21/58) after six months. Our results show that CT facet joint infiltration with ozone is a good method for treatment of lumbar facet joint syndrome. The injections can be repeated and the treatment has no side effects. The best results were seen in patients with only spondyloarthrosis of the facet joints. Facet joint ozone injection therapy using a standardized protocol is safe, effective and easy to perform. However, the clinical effect is limited (65.5% decreasing to 36.2% after six months), and we recommend repeating the injections after one to three months.

Introduction

Facet degeneration known as lumbar facet joint syndrome is a common condition, affecting about 80% of patients with low back pain. Commonly encountered in the elderly, facet joint syndrome can be the primary cause of deterioration of the motor segment and a secondary cause in the course of progressive disc degeneration subsequent to other diseases. The facet joints are related to the same elements at the spinal levels above and below them constituting synovial joints that allow the spine to carry out flexion, extension and rotation movements. Many conditions can give rise to facet joint symptoms, osteoarthritis being the most common. Osteoarthritis causes a reduction or disappearance of the joint cartilage, erosion of the adjacent bone margin, abnormal bone growth of the facets and articular processes, and lastly joint instability which may lead to vertebral subluxation. The sensory nerve endings of the facet joints and surrounding tissues are subjected to irritation which gives rise to back pain.

Patients are selected for interventional treatment on the basis of clinical examination, history-taking and diagnostic imaging. Radiological study of facet joint syndrome includes conventional x-ray examination and computed tomography scan to disclose the joint relations, abnormal growth of the joint bone component, and shrinkage of the joint spaces which is an indirect sign of cartilage rearrangement (figure 2). However, the main diagnostic imaging technique is magnetic resonance, namely T2-weighted fast spin echo sequences with fat signal suppression and T1-weighted fast spin echo sequences with fat signal suppression and administration of paramagnetic contrast medium to reveal the inflammatory process active within and around the facet joint (figure 3). The contraindications to this mini-invasive intervention include local infections at the presumed site of entry (osteomyelitis and spondylodiscitis), impossible access to the inside of the joint due to extensive solid lateral and posterolateral fusions, and neurological complications. This study assessed the therapeutic efficacy of ozone infiltration into the facet joints in patients with lumbar facet joint syndrome.

Materials and Methods

From November 2004 to December 2007, we treated 58 patients aged between 49 and 82 years (average 68.7), 42 men and 16 women present-
ing facet joint syndrome. On enrolment a clinical record was prepared for all patients recording: name, date of birth, date of enrolment, date of treatment and clinical information. Before treatment all patients enrolled in the study had under-

Figure 1  Axial CT scan with bone reconstruction algorithm: note the reduced joint interspacing with arthrotic degeneration of the facet joints (arrows). Secondary diastasis of the facet joints with a tendency to joint subluxation is evident on the right (arrowheads).

Figure 2  Axial MR scan after i.v. administration of contrast medium: lumbar facet joint syndrome causing shrinkage of the joint cartilage and erosion of the adjacent bone margin (arrows) and abnormal growth of the facet joints (arrowheads).

Figure 3  Axial MR scan after i.v. administration of contrast medium showing inter and intra-apophyseal arthritis with local inflammation (arrows).

Figure 4  A 53-year-old man with chronic low back pain mainly extending to the left side. MR scan after i.v. administration of paramagnetic contrast medium establishes a diagnosis of facet joint syndrome of the left facet joint (arrows).
gone standard spine x-ray examination followed by CT scan of the lumbosacral spine and subsequent lumbosacral MR scan with and without paramagnetic contrast agent administration (figure 4).

All patients underwent CT-guided ozone infiltration into the facet joints administered on a day hospital basis. Patients first had a preliminary CT scan to establish the point of needle insertion on the skin. Then the distance from this point to the facet joint was measured calculating the approach to the joint. Local anaesthesia was administered using ethyl chloride spray. A 22G X 9 spinal needle was used throughout. CT scans were done to ascertain the correct position of the needle within the joint capsule (figure 5). We injected 3/4 cc of oxygen-ozone gas mixture at 25µg/ml into the facet joints. Another CT scan was then done to check the correct distribution of the oxygen-ozone mixture (figure 6). Patients were kept supine and under observation for thirty minutes after the procedure and then discharged in the absence of complications. The clinical benefit of the treatment was almost immediate. Patients were then reassessed clinically using a modified McNab method at one, three and six months after treatment without further infiltration. No long-term CT scans were performed.

Results

The 58 patients we selected presented low back pain caused by facet joint syndrome resistant to all physical and pharmacological forms of management who underwent CT-guided O₂·O₃ infiltration into the facet joints. Thirty-eight (65.5%) patients obtained a complete resolution of pain immediately after treatment. Therapeutic outcome was assessed by a modified McNab method according to which excellent outcome corresponded to a complete disappearance of pain, mediocre with a partial resolution of pain and poor with no response to treatment. At subsequent clinical follow-up assessment with the McNab method the therapeutic success rate dropped to 55.1% at one month as 32 out of the 58 patients continued to have an excellent outcome, while it dropped again to 46.5% (27/58 patients) after three months and 36.2% (21/58 patients) after six months.

Discussion

The indication for O₂·O₃ infiltration into the facet joints is facet joint syndrome, irritation (arthopathy) of both joint surfaces or segmental instability due to disc degeneration. Pain is
References

1 Andreula C: Ernie discale lombosacrali: tecnica di chemio-discosi con nucloptesi con 02-03 e infiltrazione periradiocolare e periangionigare sotto guida TC. Rivista Italiana di Ossigeno-Ozonoterapia 1: 79-85, 2002.


Electromyographic Analysis of the Outcome of Lumbar Disc Herniation Treated by Intradiscal Oxygen-Ozone Gas Mixture Injection

A. ALEXANDRE, A. ZALAFFI*
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* Neurosurgery Institute, University of Siena; Siena, Italy

Key words: oxygen-ozone therapy, electromyography, intradiscal injection

Introduction

In recent years statistical analyses have shown that 65% to 80% of adults have an episode of low back pain at some time in their lives, and although most cases resolve quickly, 40% recur and 5% result in a residual disability after one year. The extremely high frequency of the problem, and the discrepancy between pathological neuro-imaging findings and clinical status both before and after open surgery have recently led to a broad review of the pathophysiology and reconsideration of the possible treatments.

Mechanisms of Disc Degeneration and Subsequent Nerve Dysfunction and Pain

Disc cells synthesize their matrix and break down existing matrix by producing and activating degradative enzymes, such as matrix metalloproteinases (MMPs) and a disintegrin and metalloproteinase (ADAMS) 1-7. Molecular markers of matrix turnover are naturally most plentiful during growth but usually decline thereafter 8. The proteoglycan content of the disc is at its peak in the young adult and declines thereafter 8 presumably because of proteolysis. Disc cells appear to adapt the properties of their matrix to suit prevailing mechanical demands, although the low cell density and lack of a blood supply ensure that changes are not as rapid or pronounced as in adjacent vertebrae 9. Adaptive remodeling probably contributes to the wide variation in compressive strength of adult discs, which ranges from 2.8 to 13.0 kN when they are tested in a manner that causes failure in the disc rather than the adjacent vertebra 10.

Injured discs show increased levels of catabolic cytokines, increased MMP activity 8,11, and scar formation 12, especially in the vicinity of anular tears 12,13. They also show evidence of renewed matrix turnover 8,14 and a more variable range of collagen fibril diameters 15. However, gross injuries to a disc never fully heal. Scalpel cuts in the outer annulus fill with granulation tissue, with only the outer few millimeters being bridged by scar tissue 16,17. Anular tears are not remodeled as in bone, presumably because the sparse cell population is unable to break down the large collagen fiber bundles of the annulus and replace them with new 18. Collagen turnover time in articular cartilage is approximately 100 years 19 and could be even longer in the disc. Proteoglycan turnover is faster, possibly 20 years 18, and some regeneration of nucleus pulposus appears to be possible in young animals 20. Injuries that affect the inner annulus or endplate decompress the nucleus 21, and healing processes are then overtaken by severe degenerative changes 15.

A series of biochemical and histologic changes have been described as typical of disc aging process. The blood supply to the vertebral endplate decreases during early childhood, and microstructural clefts and tears become common by the age of 15 years, especially in the nucleus and endplate 22. Cell density decreases throughout growth (23), and the nucleus pulposus tends to condense into several fibrous lumps, separated from each other and from the cartilage endplate by softer material 24. Proteoglycan fragmentation starts during childhood 31, and with increasing age, the overall proteoglycan and water content of the disc decreases, especially in the nucleus 17 and the collagen content increases. Fine type II collagen fibrils in the inner annulus are replaced by type I fibers as the annulus encroaches on the nucleus, and type I fibers throughout the disc become coarser. As long as
the proteoglycan fragments remain entrapped in the disc, they can fulfill a functional role similar to that of the intact proteoglycan. Reduced matrix turnover in older discs enables collagen molecules and fibrils to become increasingly cross-linked with each other, and existing cross-links become more stable. In addition, reactions between collagen and glucose lead to nonenzymatic glycation (extra cross-links that give old discs their characteristic yellow-brown appearance). Increased cross-linking inhibits matrix turnover and repair in old discs, encouraging the retention of damaged macromolecules and probably leading to reduced tissue strength. Matrix synthesis decreases steadily throughout life but sometimes increases again in old and severely disrupted discs.

All these characteristic aspects of disc degeneration are to be kept in mind when considering the nerve root disease arising from disc degeneration which provokes both physical compression on the nerve root with consequent ischemia, and metabolic intoxication. Ingrowth of nerves and blood vessels has been shown to be an important feature of structurally disrupted discs, and that would collapse hollow capillaries. Reduced proteoglycan content in old and degenerated discs may also facilitate the ingrowth of nerves and capillaries because aggrecan can inhibit their growth in vitro. Ingrowth of nerves has been thought as a possible basis for the evolution of acute pain in chronic persistent pain.

Radicular pain is often the result of nerve root inflammation and irritation. Clinical practice and research demonstrate that mechanical compression on the nerves may cause only motor deficits and altered sensation, but will not cause pain. Inflammation in the epidural space and nerve roots provoked by a herniated disc is a significant factor in causing radicular pain. Chronic compression of a nerve root can induce axon ischemia, impede venous return, promote extravasation of the plasma protein, and cause local inflammation. If dorsal root ganglia are chronically compressed and irritated, this theoretically can lead to their sensitization and resultant radicular pain. Similar mechanisms of radicular pain are postulated to occur in the thoracic and cervical spine as well. In summary, clinical practice and animal research suggest that radicular pain is the result of inflammation of the nerve root in the epidural space provoked by leakage of disk material, compression of the nerve root vasculature, or irritation of dorsal root ganglia from spinal stenosis.

### Electromyography

The classical instrument for studying nerve functioning alteration is EMGraphy. Altered EMGraphic tracings indicate the dysfunction of muscles due to inadequate transmission of electrical impulses along a peripheral nerve. A compressed or metabolically altered nerve loses its capability of active progressive point by point production and transmission of electrical impulses towards muscles. The instrument will record the dysfunction in the muscles, disclosing whether the alteration has a central or peripheral nervous system origin.

EMGraphic recording is normally associated with Electro Neurographic Recording. This consists in the recording of the conduction quality and velocity in a nerve and will demonstrate the anatomical site where the obstacle exists.

### Patients and Methods

Among patients treated by intradiscal oxygen-ozone (O₂-O₃) administration for nerve root compression in the period from January to June 2006, we randomly selected a group of 200 cases for this study. Among these, 125 patients showed signs of mono or pluriradicular nerve dysfunction (125 out of 200, 62.5%) at the time of enrolment for EMGraphic treatment. Details of the dysfunction are given in table 2.

Repeated EMGraphic control during the treatment gives a valid parameter in order to quantify nerve root dysfunction that is objective, repeatable and accurate.

The treatment consisted in intradiscal O₂-O₃ gas mixture administration at doses of 10 to 15 ml (this depends on the fissuration of the annulus and subsequent diffusion of the gas in the periradicular and peridural space) and was performed by the senior author. EMGraphic controls were per-

### Table 1: The anatomical location of nerve roots with respect to the disc level.

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<th>Nerve Roots</th>
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<th>Foramen</th>
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</tr>
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<td>LA S1</td>
<td>L5S1</td>
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formed on enrolment, and at four and 12 months postoperatively by the electrophysiologist (A.Z.) as an independent observer.

Results

The evolution of the EMGraphic picture does not always correspond to the clinical situation. In several cases normalization of clinical status will coexist with residual signs of EMGraphic dysfunction. This is notorious in radicular pathology, as well as in peripheral nervous system pathology in general, whichever kind of medical treatment was undertaken.

EMGraphic data will express the nerve structure dysfunction as a consequence of relative ischemization given by mechanical compression and by the mentioned biochemical factors which underlie the problem. Persistence of signs of damage over time will indicate that some nerve fibres are definitively altered. This may also exist in the absence of any clinical manifestation.

On the other hand, EMGraphic improvement will indicate the recovery of nerve root function, thanks to the normalized nourishment.

References

Minimally Invasive Disc Surgery
Ozonucleolysis

H. GUPTA*, V. KUMAR*, V.S. KUMAR**

* Kumar Medical Park, New Delhi and Gurgaon; New Delhi, India
** Department of Neurosurgery, Indraprastha Apollo Hospital; New Delhi, India

Key words: minimally invasive surgery, ozone discectomy, ozonucleolysis

SUMMARY - Ozonucleolysis is a least invasive non-surgical option for patients with discogenic brachalgia and sciatica who have failed to respond to conservative management. This procedure is rapidly gaining international acceptance and is well suited to the Indian environment by virtue of its efficacy, affordability and safety. This paper reviews the relevant scientific basis for ozonucleolysis.

Introduction

Back pain affects nearly 80% of all adults, with surgery at one end of the therapeutic spectrum and watchful waiting at the other. Minimally invasive disc surgery encompasses many important medical, surgical and molecular advances in the field.

The concept of minimally invasive disc surgery is the treatment of the offending pathology while preventing iatrogenic injury involved with open surgery.

The net outcome is lower morbidity and less post operative pain further associated with a shorter hospital stay. The introduction of the operating microscope into neurosurgery in 1955 by Malis set the stage for minimally invasive surgery.

In the mid-1970’s, the senior author and others began to use operating microscopes for disc surgery. This innovation of microdiscectomy was first well described by Yasargil and Caspar in 1977. Over the years, microdiscectomy has become the surgical standard of care and three randomized clinical trials have shown equivalent clinical outcomes of microdiscectomy as compared with standard discectomy.

While microdiscectomy has advantages over open surgery, it fits under the more invasive of the options of minimally invasive spine surgery (table 1). In 1983, Weber in Oslo published an eye-opening ten-year follow up of 280 patients with lumbar disc herniation showing that patients who had undergone surgery exhibited more significant pain relief at one year, but had no sustained improvement at four and ten years.

Further, results of lumbar surgery have shown a

<table>
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<td>ii. Arthroscopic approach</td>
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<td>iii. Endoscopic approach</td>
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<tr>
<td>iv. Foraminal approach</td>
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<tr>
<td>v. Laser approach</td>
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<tr>
<td>vi. Electrotherapy (Radiofrequency and IDET)</td>
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<tr>
<td>vii. Coblation</td>
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<tr>
<td>viii. Ozonucleolysis</td>
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| Extradiscal              |
| i. Microdiscectomy       |
| ii. Foraminal approach   |
| iii. Ozonucleolysis      |

<table>
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</tr>
<tr>
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<td>ii. Ozonucleolysis</td>
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</table>

| Extradiscal       |
| i. Epidural steroid injection (ESI) |
| ii. Ozonucleolysis |
Figure 1  *Model of a herniated disc.* Mechanism: Direct compression. Biochemical events and inflammatory interface: • N.O.; • PLA2, Prostaglandin; • Vascular factors; • Immune mediated; • Others.

Figure 2  *Case Study.* A 38-year-old executive presented in August 2006 with a 4 month history of disabling left leg pain starting after a game of cricket that failed to respond to anti inflammatory drugs and rest. *Clinical examination:* Straight leg raising positive to 45 degrees and weak partial foot drop on left. *MRI:* Large left L4-5 disc extrusion. *Course:* On 13/10/2006, ozonucleolysis with 4 ml intradiscal and 12 ml periradicular O₃O₂ at 29 mcg/ml, additional IM O₃O₂ injections. Complete recovery. Follow-up MRI at 6 months showed complete resolution of disc herniation.
significant failure rate of 14% to 30% depending on the study.

The remainder of this review will deal with ozonucleolysis, an innovation that is a promising alternative to invasive procedures.

Ozonucleolysis

Injection of oxygen-ozone is the least invasive alternative for cervical and lumbar discogenic radiculopathy. It was first performed in 1989 in Italy by Verga when he injected oxygen-ozone gas into the paraspinal disc to treat lumbar herniation. This procedure was further modified by Muto ten years later when he injected the oxygen-ozone mixture directly into the discal space.

We brought oxygen-ozone therapy to India in 2002 and have termed this procedure ozonucleolysis. To appreciate the mechanism of action of ozonucleolysis, it is important to begin with the etiology of sciatica.

Mechanical

Direct
- Compression of the nerve root by prolapsed disc with resulting compression on the spinal ganglion.
- Deformation and sensitization of the annular innervation in its outer fourth.

Indirect
- Ischemic changes in the nerve root from its compression of the arteria nervosa and venous congestion from compression of the draining veins. The cumulative effect of compression and venous congestion translates into oedema of the nerve root and lowers the pain threshold.
- Segmental demyelination with conduction abnormalities.

Inflammatory
- Inflammatory mediators release signaling molecules that cause the sensation of pain through injury to the neural membranes. High resolution MRI images show an intensification of the nerve root indicating the presence of inflammation. The use of epidural steroids with reasonable efficacy in many cases of disc-prolapse induced sciatica furthers the case for an inflammatory etiology of pain. An important consideration is that while the pain relief seen in ESI is temporary, percutaneous ozonucleolysis is a minimally invasive alternative to open surgery.
  - The nucleus contains a very high level of phospholipase A2 (PLA2), that when exposed to the perineural tissues and to the outer layers of the annulus produces an intensive inflammatory reaction leading to production of chemical mediators of pain such as prostaglandins and leukotrienes. Further, PLA2 is thought to cause direct damage to the nerve fibres by directly attacking the perineural and neural membrane phospholipids.
  - PGE2 is produced directly by the disc tissue and IL6 produced directly by the disc tissue and is found elevated in CSF in patients with disc protrusions.

The intervertebral disc is composed of the nucleus pulposus, cartilage and annulus. The biochemical effects of ozone have been discussed at length by Bocci. Ozone is proposed to cause the collapse of the proteoglycan structure as it transforms to the singlet oxygen state that readily oxidizes the sugar core of the nucleus. This oxidation is thought to lead to a disruption of the inter and intra-molecular bonds within the disc, causing the ultimate disc shrinkage. Further ozone has been shown to modulate various cytokines such as TNF-alpha and IL-6.

The process by which ozone may exert an anti-inflammatory effect is a topic of ongoing interest to the scientific community.

Ozonucleolysis in India

Years of neurosurgical experience have led to an appreciation of the importance of the development of lesser invasive approaches for the treatment of disc prolapse to reduce collateral damage to the adjacent nociceptive tissues, the incidence of failed back syndrome and the need for repeat surgery. To offer an affordable and minimally invasive therapy to patients, we have introduced this new technique through three international conferences and workshops in New Delhi.

We have completed over 500 cases at our free-standing pain management centers in New Delhi and Gurgaon.

The patients had lumbar and cervical radiculopathy, who otherwise would have been subjected to open surgical or another minimally invasive procedure.

All patients had failed response to adequate
rest, physical therapy and NSAIDS. Each had an MRI/CT scan proven disk herniation that varied from a contained disk to large near total extrusions. Review of the data of the first 200 patients showed a sustained successful outcome of 88% over three years of follow-up.

There is growing excitement about this low cost alternative to surgery in India.

Conclusion

Back pain is a multi-factorial disease. An important easily definable cause is disc herniation. Ozonucleolysis is an emerging modality that should be considered in the non-surgical management of herniated discs. Results from international studies have shown the promise of this technique.

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Percutaneous Paravertebral Infiltration of O₂-O₃, Bioresonance Magnetotherapy, Transcutaneous Electrical Nerve Stimulation and Psychosomatic Postural Rehabilitation in the Treatment of Degenerative Joint Disease of the Lumbar Spine with Functional Insufficiency of the Vertebral Motor Unit

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Key words: lumbar spine, degenerative diseases, ozone

SUMMARY - This study was designed to prove the effectiveness of transcutaneous electrical nerve stimulation (TENS) for the treatment and rehabilitation of degenerative joint disease of the lumbar spine with functional insufficiency of the vertebral motor unit. We treated 549 patients between the ages of 50 and 75 years, divided into four groups A, B, C and D. Group A was treated with TENS electrostimulation and psychosomatic postural rehabilitation, group B with bioresonance magnetotherapy, TENS electrostimulation and psychosomatic postural rehabilitation, group C with percutaneous paravertebral infiltrations of O₂-O₃, TENS electrostimulation, psychosomatic postural rehabilitation and bioresonance magnetotherapy. To evaluate the therapeutic effectiveness comparisons were made between groups A-B, B-C, C-D after the first 11 weeks of treatment, and at one, six and 12 months respectively. The improvements from the basal value among the groups were statistically significant (p<0.05) throughout the 11 weeks of treatment and throughout the following 12 months patients maintained significant improvements. In the A-B comparison, observations at the end of the 11 weeks of treatment showed a prevalence of improvements, and at the follow-ups at one, six and 12 months, respectively. Group A had more improvements than group B. In the B-C comparison, observations at the end of the 11 weeks of treatment initially showed a prevalence of healing and improvements in group C compared to group B. The patients in group C maintained better therapeutic effects, showing fewer regressions than group B in the first six months, followed by more loss of performance in the following six months. In the C-D comparison, observations at the end of 11 weeks of treatment showed a closely comparable improvement in both groups, with a prevalence of healing and improvements, in particular at the follow-ups at one, six and 12 months, respectively. Group D showed fewer improvements at each of the checks than did group C. Oxygen ozone therapy is a useful adjunct in the current therapy of degenerative joint disease of the lumbar spine with functional insufficiency of the vertebral motor unit, leading to pain resolution in a significant number of patients. The integration of oxygen ozone therapy with TENS, bioresonance magnetotherapy and postural rehabilitation guarantees a better maintenance of the obtained improvement over time.

Introduction

Instead of discussing the well-defined and unit pathologies of the degenerative symphyses and synarthroses of the disk (single hernias and/or protrusions of the disk), this paper takes into consideration the less well documented degenerative pathologies of the diarthroidal joints (lumbar arthrosis, or spondyl arthrosis, or disk arthrosis, or deforming spondylosis), better defined as degen-
erative joint disease of the lumbar spine with functional insufficiency of the vertebral motor unit, whose main symptoms are pain and impaired movement.

Various pathologies of back structures coexist in degenerative joint diseases of the lumbar spine with functional insufficiency of the vertebral motor unit, coexist: synarthrosis (intervertebral disk), diarthrosis (interapophysial joints), syndesmosis (intersacrospinous ligaments, intertransverse ligaments, yellow ligaments, ileolumbar ligaments) and osteoporosis.

Different abnormalities of the lumbosacral rachis come into play in this polyhedric pathology and they support the pain mediated by the spinal nerves, the laceration of a tendinous and muscular insertion, an insertional pathology of the perios- teum, the protrusion of the disk against the surrounding fibrous band (anulus fibrosus), postural problems of alignment and muscular imbalance and osteoporosis.

Through physical diagnosis we can distinguish the following fundamental forms of pain: originating in the capsules and the facet joints, originating in the nerve roots, originating in the plates, and originating in the vertebral column.

Materials and Methods

This study aimed to verify an alternative treatment for back pain without anti-inflammatory drugs, i.e. steroidal drugs, using instead magnetotheray, bioresonance, TENS electro-stimulation, postural rehabilitation, and percutaneous paravertebral infiltrations of O₂-O₃, TENS electro-stimulation, and postural rehabilitation PR.

We treated a group of 135 patients (Group A) with degenerative joint disease of the lumbar spine and functional insufficiency of the vertebral motor unit at our centre.

These patients of both sexes, between the ages of 50 and 75 years had assumed various pharmacological therapies with FANS or COX in the past, obtaining transitory benefits which had decreased with the time.

After a “wash out” period of two months, the patients were treated with a therapeutic protocol which foresaw 15 TENS electro-stimulation and postural rehabilitation PR sessions.

Because the treatment of this group had not been very effective, with a modest percentage of improvements, to verify whether other types of treatments would be successful towards improvements within the clinic study group of patients with similar clinic pathology, we requested, by informed consent, the permission to adhere to treatment protocols which foresaw a paravertebral infiltration treatment of O₂-O₃ in addition to the TENS electrostimulation and the psychosomatic postural rehabilitation, a bioresonance magnetotherapy and excluding the use of anti-inflammatory drugs.

A group of 139 patients (Group B) of both sexes between the age of 50 and 75 years were treated with: 15 sessions of TENS electrostimulation, bioresonance magnetotherapy BRT and postural rehabilitation PR.

A third group of 137 patients (Group C) of both sexes between the age of 50 and 75 years decided to follow a treatment with: 15 sessions of paravertebral infiltrations of O₂-O₃, TENS electrostimulation and postural rehabilitation PR.

A last group of 139 patients (Group D) of both sexes between the age of 50 and 75 years decided to follow a treatment with: 15 sessions of paravertebral infiltrations of O₂-O₃, TENS electrostimulation, bioresonance magnetotherapy BRT and postural rehabilitation PR.

The sessions had a twice weekly schedule for the first eight therapies and weekly for the following seven therapies.

All the patients had a nuclear magnetic resonance scan of the lumbosacral area and an osseus computerized metalometry (OCM).

Excluded from the “trial” were patients suffering from diabetes, secondary osteoporosis, and osteoporosis manifest to stages 2 and 3, clinically manifested neurological sufferance demonstrated electro-myographically.

For evaluation of clinical effectiveness, the scores of the VAS pain evaluation scale (Visual Analogic Scale) were applied, using a scale from 0 to 10, where 0 means “no pain” and 10 “the utmost pain”, and where applicable some patients were evaluated using Barthel’s pointer, using a scale from 0 to 100, where 0 means “absolute inability” and 100 “normal”. These scales were given out before treatment (basal evaluation) after 11 weeks of treatment and at one, six and 12 months respectively. In particular, in the course of the 11 weeks the improvement was evaluated considering the following parameters: Healing (0-2 VAS 100 Barthel), Good (2-4 VAS and 81-99 Barthel), Fairly good (4-6 VAS and 61-80 Barthel), Moderate (6-8 VAS and 41-60 Barthel), Unvaried (8-10 VAS and 0-40 Barthel). We also began evaluating the therapeutic response to the treatments.

In the following 12 months increasing pain was evaluated considering the following parameters: None Vague (0-3 VAS and 81-100 Barthel), Moderate Mild (4-7 VAS and 41-80 Barthel), Severe Considerable (8-10 VAS and 0-40 Barthel).

The following therapeutic methodologies were used in the study:
Oxygen Ozone Therapy

The ozone action at the level of the motor vertebral unit, is explicated at a mechanical level, reflecting stimulation of the descending antinociceptive system; and biochemical metabolic, oxidant on the double bonds of the anulus macromolecular chains, increased release of antagonists able to neutralize the pro inflammatory cytoquinine, increased release of immunoppressive cytoquinine, inhibition of the synthesis of the pro inflammatory prostaglandins and release of bradiquinine and algogen mixtures.

The applied teaching method was the infiltration through paravertebral cutaneous injection, after having identified the lesion levels. In a subject with a normal weight you would use 20 ml syringes with 23 G needles, in the event of an overweight or obese person it is more effective to use a 22 G longer needle. The gas infiltration is made in the measure of 10 ml of gas mixture per injection site. The operation is bilateral and the ozone concentration is 20 µ/ml. To find the lumbar points refer to the bisiliac line and to the relative spinous apophysis, move about 2 cm away from this apophysis and proceed to the insertion of the needle with precision and linearity of entry, which must occur with a gentle 45° inclination over the cutaneous planes, at metameric levels L3-L4, L4-L5, L5-S1. After the infiltrative therapy, you perform a mild massage to facilitate gas diffusion.

The treatment length is 15 sessions with a biweekly schedule for the first eight weeks, and weekly from the ninth application.

Transcutaneous Electrical Nerve Stimulation

Currents with low frequency and different form are used in transcutaneous electrical nerve stimulation.

Psychosomatic Postural Rehabilitation

Psychosomatic postural rehabilitation techniques are based on the fact that the postural muscles are endowed with a certain plasticity, called “tisotropy”, they respond to immobilization with an increase in rigidity, and to eccentric contraction...
or to passive extension, by reducing the rigidity. The psychosomatic postural rehabilitation model proposed takes its cue from the kinesitherapy techniques that refer to the method of Alexander, Mezieres, Souchard, Mc Kenzie, Feldenkrais and Jacobson. The proposed exercises begin with relaxation training which takes into particular consideration the correct use of abdominal respiration.

It follows postural exercise that, besides being a fundamental of modern back school, incorporates complete medical and comprehensive common exercise techniques, useful to the general improvement of postural abnormalities and pathologies, more or less directly correlated to these disorders.

We conclude with a mobilization of the lumbar spine, along with specific manipulation manoeuvres.6-11.

**Bioresonance Magnetotherapy**

According to Quantum Medicine there exists an electro-magnetic level of living matter that is in dialogue with the chemical level, assuring that the “flow” of molecules is well ordered. When this order fails, pathology arises, and manifests itself as an anomaly of the molecular structure, or as a disturbance of the controlling electromagnetic net.

Electromagnetic bioresonance is a clinical application in which pulsed magnetic waves, emitted by a magnetic field artificially produced, recreate by resonance the proper frequencies of the cells composing our organs, referred to as biological resonance.

The active magnetic fields act in consequence to induce microcurrents (electromagnetic action) and/or to direct magnetic action (magnetomechanical action).

**Electromagnetic action:** The induced micro-currents trigger ionic exchanges at the level of the membranes between intra and extra cellular environments, increasing the use of oxygen and restoring the potential of the membrane.

**Magnetomechanical action:** Through the action of polarization and migration of the cellular and mobile sub-cellular elements, also through enzymatic and cytochrome activity, diffusion of the biological membranes and influence of rapidly moving biological liquids to the vessels and the intercellular spaces.3,4,9,10,13,14,15,24.

**Results**

The comparisons among groups relative to the first 11 weeks of treatments are summarized in the following graphs:

**Comparison Group A-B. 11 weeks**

In the comparison between the two groups a proportional decrease of unchanged patients was observed at the end of 11 weeks of treatments with a prevalence of improvements in the patients of Group B compared to the patients of Group A.

The difference in the basal value between Group A and Group B was statistically significant (p<0.05) for the patients who had an improvement in the course of the 11 weeks of treatment (figure 1).

Percentage-wise, referring to the patients of Group B, the effective therapeutic gain was significant for the good, fair and moderate improvements, with a significant decrease in percentage for the unchanged. None of the patients in either group presented recovery (figure 2).

The following graph shows the progress in percentage of the therapeutic response during the 11 weeks of treatment (figure 3).

**Comparison Group B-C. 11 weeks**

In the comparison between the two groups a significant decrease in the percentage of unchanged, and a significant prevalence of improvements was observed at the end of the 11 weeks of treatment in the patients of Group C compared to those of Group B. The difference in the basal value between Group B and Group C was statistically significant (p<0.05) for the patients who had an improvement in the course of the 11 weeks of treatments (figure 4).

Percentage-wise, referring to the patients of Group C, compared to those patients of Group B, the effective therapeutic gain was strongly significant for the patients who showed an effective recovery and a good improvement, and significant for those who show fair and moderate improvements. From a proportional point of view, the decrease for the unchanged was highly significant (figure 5).

The next graph shows the progress in percentage of the therapeutic response during the 11 weeks of treatments. It should be emphasized that there were appreciable percentages in significant anticipation of the therapeutic response in the patients of Group C compared to those of Group B (figure 6).

**Comparison Group C-D. 11 weeks**

Percentages of data on closely comparable results in the two groups of patients.

There was a significant percentage increase in
recoveries, and improvements with total values of 72.7% at the end of the 11 weeks of treatment in Group D.

The following graphs depict the comparisons between Groups A-B, B-C and C-D relative to the next 12 months of treatment.

Comparison Group A-B. 12 months
24 patients of Group A. 50 of Group B showed an improvement

The difference in the basal value between Group A and Group B was statistically significant (p<0.05) for the patients evaluated after the 11 weeks of treatment for the next 12 months (figure 7).

In the comparison between the two groups it was observed, in the course of the year and on the follow-ups at one, six and 12 months respectively, that as regards no, vague, mild, and moderate increasing pain, there was a prevalence of patients of Group B compared to those of Group A. On the considerable and severe increasing pain there was an inversion in the comparison on percentages, in the sense that this was prevalent for patients of Group A compared to those of Group B.

The patients of Group B maintained more therapeutic effects, presenting a minor increase of pain over time, compared to those of Group A.

Comparison Groups B-C. 12 months
50 patients of Group B. 98 of Group C showed an improvement

The difference in the basal value between Group B and Group C was statistically significant (p<0.05) for the patients evaluated after 11 weeks of treatment over the next 12 months (figure 8).

In the comparison between the two groups two progressions were observed which tended to change over time.

At the follow-ups at one and six months, as regards no, vague, mild and moderate increasing pain, there was a prevalence of percentages of patients of Group C compared to those of Group B.

On the considerable and severe increasing pain
an inversion of the comparison of percentages was observed, in the sense that this was prevalent in the patients of Group B compared to those of Group C.

At the follow-up at 12 months as regards no, vague, mild and moderate increasing pain, there was a decrease on percentages of the patients of Group C compared to those of Group B, whereas in the considerable and severe increasing pain evaluations an increase was observed in percentages of the patients of Group C compared to the patients of Group B.

The patients of Group C maintained more therapeutic effects, presenting a minor increase of pain over time, compared to those of Group B, in the first six months, showing more loss of performance over the next six months.

Comparison Groups C-D. 12 months
98 patients of Group C. 101 of Group D showed an improvement

The difference in the basal value between Group C and Group D was statistically significant (p>0.05) for the patients evaluated after 11 weeks.
of treatment for the next 12 months (figure 9). In the comparison between the two groups it was observed in the course of the year and at the follow-ups at one, six and 12 months, respectively, that as regards no, vague, mild and moderate increasing pain, there were closely comparable percentages of patients of Group D compared to those of Group C. On the considerable and severe increasing pain evaluations an inversion of the comparison on percentages was observed in the sense that this was prevalent for the patients of Group C compared to those of Group D. Patients of Group D maintained more therapeutic effects, presenting a minor increase of pain over time compared to those of Group C.

Conclusions

The data analysis shows that the multidisciplinary approach with therapeutic integrated aids is very effective in the treatment of degenerative joint disease of the lumbar spine, with functional insufficiency of the vertebral motor unit. In particular, data on the positive effects of a treatment with TENS and RP in Group A, even though significant, showed a relatively low increase in percentage of improvements at the end of 11 weeks of treatment, with the value of 17.8%, with a reduction of benefits obtained within the next 12 months. Indeed as regards the increasing pain the following was observed at one month among these patients 29.17% of no vague, 25% of mild - moderate, 45.83% of considerable severe; at six months 25% of no vague, 25% of mild moderate, 50% of considerable severe; at 12 months 25% of no vague, 20.83% of mild moderate, 54.17% of considerable severe. In Group B, treated with TENS, RP and BRT, in terms of percentage, it was observed that the resulting improvements were numerous at the end of the 11 weeks of treatment, with values of 36.2%, with a greater percentage of improvements maintained over the next 12 months. Indeed as regards the increasing pain observed at one month among these patients 39.60% of no vague increasing pain, 37.76 % mild moderate, 22.45% considerable severe; at six months the data on percentages were 38.78%-66.73% and 24.49 % respectively, for no vague, mild moderate and considerable severe; at 12 months 28.57% of no vague, 27.55% of mild moderate. Indeed as regards the increasing pain observed at one month among these patients 39.60% of no vague increasing pain, 37.76 % mild moderate, and 21.78% considerable severe; at six months data of percentages were 38.61-37.62 and 23.76%, respectively, for no vague, mild moderate and considerable severe. Lastly, Group D, treated with TENS, RP, BRT and oxygen ozone therapy, presented closely comparable behaviour to Group C in the course of 11 weeks of treatments, showing a significant increase in percentages of recoveries and improvements with total values of 72.7%. The patients of this group noticed a greater persistence of improvements in the following 12 months, compared to the patients of Group C. Indeed as regards the increasing pain observed at one month, 39.80% of these patients presented no vague increasing pain, 37.76 % mild moderate, and 21.78% considerable severe; at six months data of percentages were 38.61-37.62 and 23.76%, respectively, for no vague, mild moderate and considerable severe. At 12 months 38.61% of no vague, 35.64% of mild moderate, 27.72% of considerable severe. This better response of Group D compared to Group C, referring to a longer persistence of improvements over the next 12 months, confirms the therapeutic effectiveness of electromagnetic bioresonance on the neuro, osteo and muscular problems. In Group C, treated with TENS, RP and oxygen ozone therapy, a significant increase in percentages of recoveries was observed at the end of 11 weeks of treatments and improvements with total values of 71.5% presenting solid improvement after the first six months of treatments. As regards these patients, it was observed that at one month 39.80% presented no vague pain increases, 37.76 % mild moderate, 22.45% considerable severe; at six months the data on percentages were 38.78%-66.73% and 24.49 % respectively, for no vague, mild moderate and considerable severe; at 12 months 28.57% of no vague, 27.55% of mild moderate. As regards these patients, it was observed that at one month 39.80% presented no vague pain increases, 37.76 % mild moderate, 22.45% considerable severe; at six months the data on percentages were 38.78%-66.73% and 24.49 % respectively, for no vague, mild moderate and considerable severe; at 12 months 28.57% of no vague, 27.55% of mild moderate. As regards these patients, it was observed that at one month 39.80% presented no vague pain increases, 37.76 % mild moderate, 22.45% considerable severe; at six months the data on percentages were 38.78%-66.73% and 24.49 % respectively, for no vague, mild moderate and considerable severe; at 12 months 28.57% of no vague, 27.55% of mild moderate.

In the current therapy of degenerative joint disease of the lumbar spine, with functional insufficiency of the vertebral motor unit, oxygen ozone therapy is a useful adjunct in resolving pain in a significant percentage of cases. The integration of oxygen ozone therapy with TENS, bioresonance magnetotherapy and postural rehabilitation guarantees a better maintenance of the obtained improvement over time.
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Ozone Therapy: a Clinical Study on Pain Management

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Key words: ozone, pain, sport injury, oxygen-ozone therapy, low back pain, sciatica, radiculopathy

SUMMARY - Ozone therapy has been widely used in many countries for many years and has recently continued to spread in the wake of an increasing number of basic and clinical papers published in international journals. Many of the basic mechanisms of ozone action are now well outlined. In addition, the modulation of interleukin productions and of some biochemical pathways related to inflammation and pain indicate the rationale of ozone use in many pathological conditions related to pain. This paper reports on data collected in patients treated in the last three years for pain-related disorders due to sport injury (232 subjects) or inflammatory disorders (770 subjects). The evolution of patients was followed using the Overall Patient Satisfaction Scale. The maximal score (8-10) corresponding qualitatively to “very good” was reached in 80% of patients. A rapid and sustained success was reached in pubalgia to a score 8-10 as soon as therapy was started. A progressive evolution in time was reached to a score 8-10 in patients with pain from inflammatory disorders. However, the maximal score in inflammatory joint diseases was 6-8 (qualitatively “good”). No side-effects were recorded at short and long-term follow-up. In our experience, O$_2$-O$_3$ treatment of pain and inflammatory diseases has revolutionized the management of pain caused by radiculopathy and joint disease.

Introduction

In recent years attention has focused on the use of medical ozone and on its rationale in pain management. Despite ample clarification, confusion persists concerning its potential toxicity as an oxidant agent versus the reported clinical efficacy. This confusion is a major factor preventing a more widespread acceptance of ozone administration. In addition, the use of ozone in deferens specialities like neurology, orthopaedics, internal medicine, sport medicine, endocrinology and others makes it difficult to categorize ozone as a therapeutic agent. This may cause conflict between the different fields of application and the various medical areas.

Ozone is most commonly associated with disc herniation and its efficacy is mainly linked to its peculiar effects on the biohumoral environment. Evidence that antioxidant enzymes, nitric oxide pathways and other subcellular activities could be modulated by low ozone doses is now proven and could support the surprising effects of ozone in many pathological conditions. Moreover, many biologic effects have been attributed to ozone: increased glycolysis, effects on red blood cells, effects on rheology, bactericidal, fungicide and virustatic effects, immunomodulating action and analgesic and anti-inflammatory effects. This broad spectrum of action explains the diversity of indications for medical ozone administration.

In the light of the report by Wentworth et Al, the scientific data reported could be scientifically emphasized and pharmacologically indicative. They demonstrated the physiological presence of an ozone-like mediator during inflammation, indicating ozone as a new bio-molecule with striking effects which must be considered and studied following new strategies with newly constructed randomized standardized clinical studies. Moreover, the mechanisms of action of ozone on blood bio-molecules with the generation of several messengers responsible for biological effects has been well clarified since 2002.

Nerve root pain and low back pain are some of the commonest conditions affecting the lumbar spine. Around 80% of the population in western countries will experience at least one episode of low back pain in their lifetime and 55% suffer from low back pain associated with radicular syndromes. Back pain is often caused by disc disease even though other factors are responsible for nerve root syndromes and should be relieved when
clinical symptoms fail to correlate with Computer Tomography (CT) and/or Magnetic Resonance (MR) findings.

This paper reports our experience between October 2004 and October 2007 with 1002 patients suffering from pain caused by joint inflammation, sport trauma or other inflammatory diseases treated with oxygen / ozone.

Materials and Methods

Study Design

This is a retrospective clinical trial approved by an institutional review board (Scientific and Ethics Committees of the Institution) in accordance with the principle of the Declaration of Helsinki (1997). All patients signed an informed consent form before being enrolled. All patients were given adequate information (characteristics of the study, benefits and possible side effects). Before enrolling, all participants attended a training program to familiarise with the study objectives and treatment plans. Adult patients of both genders and different ethnic backgrounds with a diagnosis of joint pain (including: knee, shoulder, cervical, lumbar spine or low back pain), sport trauma or other inflammatory diseases associated with physical pain attending the Medinat Clinic (Ancona, Italy) between October 2004 and October 2007 were eligible to participate in the study. The following exclusion criteria were adopted: severe septic conditions, hypersensitivity to the medication to be used, hepatic dysfunction, renal failure (serum creatinine level >1.32 µmol/L), pregnancy, cancer or other serious disease, inability to cooperate with the requirements of the study, recent history of alcohol or drug abuse, current therapy with any immuno-suppressive agent or anticonvulsant, concurrent participation in another clinical study or current treatment with an investigational drug. CT/MR evidence of a herniated disc fragment with symptoms of motor and/or sphincter disturbance or CT/ MR evidence of disc herniation corresponding to clinically severe motor deficit and/or sphincter disturbance. Patients were treated twice a week with an O₂-O₃ mixture (generated just before administration by an OZONOSAN APLHA PLUS device, Germany) in 12-15 consecutive sessions (with an ozone dose of 25-50 mL, ozone concentration: 8-12 µg/L, 3-5 mL per application). Ozone obtained from medical grade oxygen representing about 0.4-12 µg/L, 3-5 mL per application). Ozone was measured using a built-in UV spectrophotometer at 254 nm. Percutaneous injection was done using 30 mL disposable syringes (ozone resistant) and 30 G×1/2 disposable needle inserted in the surroundings of the affected area (local puncture). An alternative procedure was: 1) Local O₂-O₃ application (direct O₂-O₃ gas 20-40 µg/mL immersion was applied inside a sealed, ozone resistant plastic bag). 2) Major autohemotherapy (under strict aseptic conditions, 100-150 mL venous blood were withdrawn from the patient and transferred to a vacuum flask with sodium citrate, where the medical O₂-O₃ 20 µg/mL gas mixture was added to it extracorporeally in a closed, sterile pressure-free system before being reinfused via drip infusion). 3) Minor autohemotherapy (done by collecting in a 10 mL syringe 5 mL of the subject’s blood, adding an ozone dose of 0.4 mg in 4 mL of gas, mixing it quickly and injecting it intramuscularly). 4) Rectal ozone insufflations (O₂-O₃, 10-25 µg/mL, volume 50-100 mL was applied using 50 mL silicone-coated disposable syringe and rectal catheter). Ozone inhalation was avoided during the treatment.

Many different protocols are used for objective analysis of clinical results in patients with pain. We evaluated the symptoms and evolution of patients using the Overall Patient Satisfaction Scale (OPRS)⁴⁹. OPRS is based on the full patients satisfaction, and consists in a set of values from 0 to 10; 0 is attributed to the basal status (before treatment). This scale is not only linked to clinical symptoms, but also involves the patient’s impression on therapy accessibility, doctor trust and the general impression about how the treatment is conducted. Evaluation at two weeks; one, six months and one, two years was performed in all patients. The OPRS scale establishes a link between quantitative and qualitative estimation of the evolution as follows: 0-2, imperceptible; 2-4, minimum; 4-6, medium; 6-8 good; 8-10, very good.

Statistical Analysis

The OUTLIERS preliminary test for detection of error values was initially applied. Then data were analyzed using Shapiro-Wilks W test followed by homogeneity variance test (Levene). In addition, descriptive statistics were done. Results are presented as means ± standard error or median / minimum-maximum. Mann-Whitney U test was applied to detect significant differences before or after treatment. The level of statistical significance employed was p<0.05. The SPSS software package was used for all statistical analyses.

Results

General characteristics of the patients involved in the study. Baseline characteristics (table 1) of patients showed that sport trauma was most
frequent in young people (16-46 years). Patients treated to relieve pain derived for inflammatory disorders (PDI) involved a broad spectrum of ages (14-97 years), but the incidence was higher around 57 years. Males were most affected by sport injuries (80%). However no statistical difference (p>0.05) was noted between genders in PDI. Analgesic and anti-inflammatory therapy was concomitant in 23%-33% of patients, physical therapy in 14%-25%, a minor incidence was detected in the use of vitamins or supplements (1%-6%).

Hypertension accompanied 18% of patients with PDI; in addition 5% of patients had undergone surgical operations (essentially PDI patients 6%). Hypertension, renal dysfunction, diabetes or cardiovascular diseases were not detected in subjects with sport trauma. A mean of 10-12 sessions of O₂-O₃ treatment were held to reach therapeutic success. Local procedure (local puncture) was the main important clinical protocol used. Combination with a systemic procedure had a low incidence in subjects with sport injury compared to PDI patients. All patients enrolled were caucasian.

A total of 1467 patients (rates of 490 patients per year in all categories) were treated in the three years of the study with ozone therapy (figure 1), at a rate of 334 patients per year. The total proportion or the proportion among the different categories did not differ significantly (p<0.05) each year. PDI were the most common pathologies (68%), 1002 patients were treated during the time of the study. Diseases classified as PDI (not related to sport activities) included different pathologies, the most frequent being back pain. The pain most frequently originated from: lumbago, sciatica and disk herniation (including 25 patients previously treated by surgery).

Table 1 Baseline patient characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (n=1002)</th>
<th>Sport Injury (n=232)</th>
<th>PDI (n=770)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>56</td>
<td>30*</td>
<td>57</td>
</tr>
<tr>
<td>Minimum</td>
<td>14</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Maximum</td>
<td>97</td>
<td>46*</td>
<td>97</td>
</tr>
<tr>
<td>Gender (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>46</td>
<td>20*</td>
<td>48</td>
</tr>
<tr>
<td>Male</td>
<td>54</td>
<td>80*</td>
<td>52</td>
</tr>
<tr>
<td>Concomitant treatment (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analgesic/Anti-inflammatory</td>
<td>32</td>
<td>23</td>
<td>33</td>
</tr>
<tr>
<td>Vitamins/Supplements</td>
<td>1</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Physical therapy</td>
<td>14</td>
<td>26</td>
<td>14</td>
</tr>
<tr>
<td>History No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>51 (5)</td>
<td>1 (0)*</td>
<td>50 (6)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>138 (14)</td>
<td>0*</td>
<td>138 (18)</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>9 (1)</td>
<td>0*</td>
<td>9 (1)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>14 (1)</td>
<td>0*</td>
<td>14 (2)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>17 (2)</td>
<td>0*</td>
<td>17 (2)</td>
</tr>
<tr>
<td>Number of sessions, median (min, max)</td>
<td>12 (4-20)</td>
<td>10 (5-16)</td>
<td>12 (4-20)</td>
</tr>
<tr>
<td>Local procedure (LP/B%)</td>
<td>89/67</td>
<td>100/65</td>
<td>90/67</td>
</tr>
<tr>
<td>Systemic procedure (H/M/R%)</td>
<td>44/39/62</td>
<td>15/30/0*</td>
<td>44/39/62</td>
</tr>
</tbody>
</table>

Table Legend:
a) Previous surgical intervention on the affected side.
b) Hypertension was defined as elevated systolic (>140 mm Hg) and/or diastolic (>90 mm Hg) blood pressure.
c) Renal dysfunction: increase in serum creatinine >133 µM.
d) Fasting overnight plasma glucose concentration range 3.58-5.6 mM.
e) Cardiovascular disease was diagnosed by thorough history-taking and physical examination.
Note: * significant statistical differences (p<0.05) between the sport injury group compared to total or PDI groups.
Clinical evaluation

According to the OPRS scale, the clinical evolution of the joint pain inflammatory disorders treated with ozone (figure 2) showed an improvement in vertebral and articular diseases. Patients classified with a diagnosis of “back pain” involved: disc herniation (25 previously treated with surgery), lumbago, sciatalgia and others. Those included in “cervical pain” were patients with disc herniation (four previously submitted to surgery), back ache and other related pathologies.

In vertebral pain (back and cervical pain) a sustained increase in clinical status was achieved in patients (figure 2A). Just two weeks after the first treatment a significant (p<0.05) increase in clinical status was reached. Patients went from “imperceptible” (OPRS=0) to the “minimum-medium” category (back pain OPRS 3-5 and cervical pain OPRS 4-6). During the one to six months of evolution, patients reached the “medium-good” category (back pain OPRS 5-8 and cervical pain OPRS 5-7) with a significant (p<0.05) increment compared to the basal status and the evolution at two weeks. Finally, at one to two years of evolution, both groups reached the maximal OPRS category of “very good” (back pain OPRS 8-10 and cervical pain OPRS 7-9) with a significant (p<0.05) improvement compared to the basal status and the previous evolution periods.

In joint pain (knee and shoulders) a satisfactory evolution was also observed (figure 2B). A sustained and significant (p<0.05) improvement was noted in both cases up to six months of evolution. However, after one to two years patients with shoulder pain obtained better results (OPRS “good” min 4 - max 10) than patients with knee pain (OPRS “medium-good” min 2 - max 9). The variability of the ozone effect in those cases was higher than in patients with pain of vertebral origin.

In non articular pain disorders (figure 3) a significant (p<0.05) positive O₃ therapy response was also noted. Tendinitis and miscellaneous non articular pain/inflammation at one to two years of evolution obtained the OPRS category “good” (tendinitis OPRS min 5-max 9 and others OPRS min 8-max 9). An exceptional and sustained favourable evolution was observed in pubalgia just two weeks after treatment a significant (p<0.05)
evolution reached the maximum category (OPRS 6-10). Two years after ozone therapy the OPRS for pubalgia reached the maximum score (8-10).

No adverse effects were observed during ozone therapy in any of the patients (1467) treated during the last three years at the Medinat Clinic.

Discussion

The triatomic oxygen molecule known as ozone is becoming increasingly important both in an environmental context and in medicine. As regards the environment, two issues are the topics of discussion: first, the natural ozone in the atmosphere acting as a protective layer or filter to the short-wave, high-energy ultraviolet radiation coming from the sun and its man-made breakdown, forming the ozone gaps over the Arctic and Antarctic; second, the other form of anthropogenic ozone, i.e. the so-called summer smog, which is a building block for other photo oxidants or helps to form chemical radicals, all of which can be respiratory poisons. Both of these complex problems are bound up with health risks and the resulting medical consequences. In the first case, humans are endangered by a constant increase in intensive UVB radiation causing erythemas and melanomas, in the second case there is now a hazard of subjective disturbances and pathological changes to lung function and extrapulmonary organs in persons at risk due to their ozone hypersensitivity.

The known strong reactivity of ozone has contributed to establishing the dogma that ozone is always toxic and its medical application must be proscribed. Although it is less known, judiciously practiced ozone therapy is becoming very useful both on its own and applied in combination with orthodox medicine in a broad range of pathologies. Clinical results available so far have shown that properly performed ozone therapy appears useful in many diseases. In 1997 the biomedical database (MedLine-PubMed) accumulated only two papers on ozone therapy (clinical trials), whereas 243 articles were found in 2007 (figure 4). In 2007 the Cochrane database found 266 (cumulative record) articles on this topic. The main targets of ozone therapy in clinical trials are infection, inflammation, surgical intervention, pain, ischemia and vascular disorders (figure 5). Alfred
Nobel was prescribed nitroglycerine, one of the key components of dynamite, to ease his chest pain when he contracted heart disease. It took 100 years until it was clarified that nitro-glycerine acts by releasing nitric oxide gas. However, it also paved the way for medical articles detailing the biological activity of nitric oxide (NO) which are now flooding scientific journals at a rate of 500 per month. Like NO, articles dealing with the therapeutic use of ozone have been growing each year and the only hope we have is that this rapid progress of research will bring more benefit for human health.

In the last few years several articles have focused on O2-O3 treatment of patients with low back pain, cervical or lumbar disc pathology and joint related pain. In general the observed clinical effects of O2-O3 are comparable to or greater than those of traditional therapy. The low costs of O2-O3 therapy and the lack of any complications or collateral effects make this minimally invasive procedure safe and useful for the treatment of different diseases.

Our results shown a satisfactory evolution in all patients treated, including those with pain or inflammation originating from joint disorders or cases not related to joint inflammation. The efficient evolution of cases of pubalgia just two weeks after treatment, with a stable clinical status, should be connected, at least in part, to the germicide properties of ozone due to the link between pubalgia and sepsis.

Patients treated for PDI were older than those with sport trauma, probably because degenerative or joint diseases are more frequent with age. In addition, male accounted for a high proportion (80%) of patients with sport trauma. This increment should be related to the fact that sports practiced by men are more susceptible to trauma.

Regarding disk herniation, the so-called nerve-root conflict, most of the ozone actions are linked to its peculiar effects on the biohumoral environment. The mistake of considering ozone a simple mechanistic agent causing lyses and a reduction of the herniated disk persists. The major success, considered as scientific proof of the use of ozone in neuroradiology, is mostly linked to the possibility to estimate statistically the reduction or disappearance of the anatomical protrusion. In our opinion this is not enough, and a follow-up considering the status of the patient following the treatment could better indicate the efficacy of the ozone treatment. A satisfactory evolution was reached in all cases of disk herniation treated at Medinat (318 cases) using the paravertebral technique, avoiding the potential risk of other procedures (intradiscal, epidural or intraforaminal injections). Some patients (29 cases) had previously undergone surgery, indicating that this invasive procedure should be reserved to patients who fail to respond to alternative procedures like O2-O3 treatments. In pain from disk herniation, ozone therapy obtains clinical success in 80% of cases.

The variability of the clinical responsiveness of patients introduces further difficulties in designing standardized studies. A therapeutic dose of ozone can upregulate the synthesis of antioxidant enzymes and hemoxygenase. In all cases the synthesis of enzymes requires the presence of micronutrients. Indeed, recent advances in ozone effects suggest a key role of trace elements. Studies are underway to evaluate the role of Se, Mn, Cu, Zn and other essential elements for the enzymatic activity of superoxide dismutase (SOD) and other enzymes involved in the ozone effect. A dietary insufficiency or impairment either in food supply or metabolic pathways may play a negative role in the efficacy of the ozone treatment. Another reason for the variability of the clinical responsiveness to O2-O3 therapy comes from the lack of an appropriate clinical diagnosis of the redox status. Patients with severe disruption in the redox systems may not respond to the oxidant stimulus of ozone.

In the light of the latest pharmacological knowledge we can consider ozone a pro-drug which, at certain non-toxic doses, can induce a rearrangement of the biochemical pathways with the activation of a second messenger in a cascade with a multiple system action.

The ischemic preconditioning represents the best similarity in this context. Evidence that antioxidant enzymes, nitric oxide pathways and other sub-cellular activities could be modulated by low ozone doses is now proved and could support the surprising effects of ozone in many pathological conditions.

Pain is a subjective symptom of major clinical importance as it is often this complaint that motivates patients to seek treatment. The non steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen and others are among the most frequently prescribed drugs. In particular, NSAIDs have proven to be highly effective in relieving inflammation and pain caused by arthritis. NSAIDs act through the inhibition of cyclooxygenases and therefore diminish prostaglandin production. In chronic pain management the adverse effects of NSAIDs become the main drawback. A large number of inflammatory and signalling substances, such as tumour necrosis factor and interleukins (interleukin-1beta, interleukin-6, and interleukin-8), may also play a role in the development of sciatica, hernia-derived pain and back pain. Independent of nociceptor stimulus,
pain impulses are conducted through myelinated A delta fibers and unmyelinated C fibers to the dorsal root ganglion and continue by way of the spinothalamic tract to the thalamus and the somatosensory cortex. In response to stimulation of the nociceptors in the disc, the somatosensory system may increase its sensitivity, resulting in a non-functional response; i.e., normally innocuous stimuli may generate an amplified response (peripheral sensitization). When disc degeneration leads to a disc herniation, the adjacent nervous system structures, such as the nerve roots or the dorsal root ganglion, can be affected causing neuropathic pain of mechanical or biochemical origin. Disc degeneration also influence other spinal structures, such as facet joints, ligaments and muscles, which can also become pain generators. Thus, disc degeneration may be responsible for the development of chronic low back pain without being the actual pain focus.

Peripheral sensitization should be avoided by ozone or ozone mediators. Recent studies have provided strong evidence that ozonized LDL inhibited NF-kappaB and IRAK-1-associated signalling which may impair immune function.

A similar mechanism should function in ozone therapy. The oxidation of interleukin, interleukin receptors or nuclear factors should block COX2 expression and as consequence the biochemical pathway of pain. In fact, in the Medinat clinical experience, radiological evidence may or may not be relevant in patients with pain derived from radiculopathy. However 80% of success is achieved in pain derived from radiculopathy. Furthermore, recent scientific data demonstrated the physiological presence of ozone-like mediators during inflammation, indicating ozone as a new biomolecule endowed with striking effects which must be considered and studied following new strategies with newly constructed randomized-standardized clinical studies.

In our experience, O₂-O₃ treatment of pain and inflammatory diseases has revolutionized the approach to radiculopathy and articular disease pain management. O₂-O₃ is safer, cheaper and easier to repeat than treatments currently in use. In addition, O₂-O₃ therapy does not preclude later recourse to surgery should patients fail to benefit. The technique is also reliable and compatible with other procedures.

Acknowledgements

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References


Oxygen-Ozone Treatment of Carpal Tunnel Syndrome. Retrospective Study and Literature Review of Conservative and Surgical Techniques

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Key words: carpal tunnel syndrome, ozone therapy, oxygen-ozone therapy, conservative management, local steroid injection

SUMMARY - Carpal tunnel syndrome (CTS) is a neuropathy caused by median nerve entrapment under the transverse carpal ligament at the wrist. It is a common condition presenting with pain (especially at night), paraesthesia and in advanced disease muscular hypertrophy and functional deficit. Diagnosis is based on clinical findings and mainly electromyography. The use of wrist-hand appliances is decisive in patients with acute CTS to reduce pressure within the carpal tunnel. Oral NSAIDs and methylprednisolone have proved effective short-term treatments. Local steroid injection is indicated in patients without major electromyographic abnormalities, persistent paraesthesia, impaired sensitivity, weakness or hypertrophy of the thenar eminence. Infiltration of oxygen-ozone gas mixture in the same patients has yielded short, medium and long-term outcomes similar to those following steroid injection. A small group of patients maintained the therapeutic benefit two years after treatment. Unsatisfactory response to local oxygen-ozone treatment is an indication for surgery.

Introduction

Carpal tunnel syndrome (CTS) is a neuropathy caused by median nerve entrapment under the transverse carpal ligament at the wrist. The syndrome is characterized by worsening symptoms, initially mainly at night and subsequently persisting throughout the 24 hours. Surgical management is indicated for the more severe forms characterized by continuous symptoms and sometimes associated with hypotrophy of the thenar eminence, whereas mild and moderate forms usually benefit from conservative treatment. The aim of this study was to assess the therapeutic efficacy of infiltrations of a balanced Oxygen-Ozone (O₂-O₃) mixture injected within the carpal tunnel in patients with mild and moderate CTS.

Materials and Methods

This retrospective study evaluated 112 patients (80 women, 32 men) aged between 27 and 79 years (average 51) who underwent O₂-O₃ treatment between March 2003 and November 2006. Seventy-four patients had bilateral disease for a total of 186 hands treated.

Clinical diagnosis was confirmed by electromyography. Patients with clinical signs of muscular atrophy were excluded from the study.

The study protocol included administration of 2-3 ml of balanced O₂-O₃ mixture at a concentration of 10 mg/ml injected beneath the transverse carpal ligament. Ten ml syringes and 27G needles were used. The injection was made medially to the long palmar tendon with the needle caudally inclined at 45° to a depth of 1-2 cm after aspiration being careful to slightly withdraw the needle after having evoked paraesthesia to avoid administration within the sheath of the nerve itself.

The treatment cycle included two weekly administrations for five weeks for a total of ten sessions followed by a further two administrations two weeks and one month later.

Results were assessed at the end of treatment and one year later on a four level pain-function scale: 1. Excellent, 2. Good, 3. Satisfactory, 4. Absent.
Results

The results of the study are summarized in table 1. At the end of treatment 90% of treated hands had a good-excellent improvement in hands treated; only 6% had no benefit. Improvements were significantly maintained at one year follow-up (87%).

During the O₂-O₃ treatment significant clinical results were evident after three to four injections (table 2). Half the patients had a good-excellent reduction of pain at the sixth treatment session. At the end of treatment none of the patients presented a worsening of symptoms requiring surgery. Patients in whom the response to O₂-O₃ treatment proved unsatisfactory were given alternative treatments. At one year follow-up (table 3) seven patients had undergone surgery to one hand; three of them had had a satisfactory response to ozone therapy in the other hand. Only four patients opted for surgery to both hands. In all cases the decision to undergo surgery was based on failure to respond to treatment.

Discussion

Carpal tunnel syndrome (CTS) is a peripheral neuropathy commonly encountered in clinical practice. CTS is more frequent in women aged between 40 and 60 years, occasionally also in patients under the age of 20 years. A prevalence study undertaken by De Krom ¹ reported a CTS rate of 3.4% for women and 0.6% for men. The disorder is idiopathic in more than two thirds of cases ². Secondary forms are associated with a vast range of diseases: diabetes mellitus, hypothyroidism, pregnancy, obesity, oestrogen therapy, rheumatoid arthritis, gout, amyloid disease, and recurrent microtraumas (use of vibrating instruments) ²,³. CTS is bilateral in around 70% of cases with a prevalence in the dominant hand ². Symptoms include paraesthesia and cutaneous sensory loss associated with a sensation of swelling in the hand, mainly in the first three fingers and partly in the fourth finger, especially at night. Symptoms very often do not present a typical distribution and all fingers of the hand are commonly involved ⁴. Disease evolution consists in a progressive reduction in sensitivity in the affected fingers followed by muscular hypotrophy. CTS is caused by median nerve entrapment as it passes through a fibrous bony channel, the carpal tunnel, formed by the carpal bones over which the transverse carpal ligament is stretched. The ligament is a fibrous ribbon inserted on the scaphoid and trapezium bones on the one side and the pisiform and uncinate bones on the other. The carpal tunnel is crossed by nerves, blood vessels and tendons.

CTS diagnosis is based on history-taking, symptoms evoked by manoeuvres increasing pressure within the carpal tunnel (Phalen and Tinel tests) but mainly by electrophysiological study of the median nerve, and to a lesser extent ultrasound and MR scans of the carpal channel.

In 1998 Ferry et al demonstrated that the diagnostic gold standard for CTS is nerve conduction study of the median nerve by EMG ⁴. In particular, for diagnosis they cited a temporal latency >3.7 ms for sensory conduction speed and >4.5 ms for motor conduction speed. With respect to this gold test, the classic tests of Phalen and Tinel are less reliable with a sensitivity of around 25% making them unfeasible in case of a negative result ⁵,⁶. The authors undertook a well-designed study to test the following hypothesis: “the more typical the symptoms are, the greater the association with electromyographic diagnosis”. They sent patients

<table>
<thead>
<tr>
<th>End of treatment 12 months</th>
<th>Excellent</th>
<th>Good</th>
<th>Satisfactory</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
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</tr>
<tr>
<td>146 (78)</td>
<td>22 (12)</td>
<td>7 (4)</td>
<td>11 (6)</td>
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<tr>
<td>130 (70)</td>
<td>32 (17)</td>
<td>11 (6)</td>
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<table>
<thead>
<tr>
<th>Good/Excellent</th>
<th>Treatment session</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>II</td>
</tr>
<tr>
<td>3%</td>
<td>25%</td>
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</table>

<table>
<thead>
<tr>
<th>Surgical treatment</th>
<th>End of O₂-O₃ treatment</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (%)</td>
<td>15 (6%)</td>
<td></td>
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</table>
a postal questionnaire with a diagram of the hand to gain feedback information on the presence of symptoms or not and on their anatomical distribution. In addition, they studied the EMG and the distribution of symptoms comparing the questionnaire findings with the presence of EMG changes in 155 patients, of whom 115 presented symptoms and 40 did not. The first surprise was that 20% of asymptomatic patients had an altered EMG tracing, whereas only 18% had classical symptoms and an altered EMG while 14% had possible symptoms and an altered EMG (17.4% in all). CTS is therefore a common disorder but clinical features are imprecise. In other words, the decision to treat based on clinical findings alone means relying on the high casual prevalence of the condition (17%), with a risk of pointless treatment of around 83% for conservative forms of management and an even greater risk for surgery. Early diagnosis of CTS will allow prompt preventive measures to be instituted with appropriate conservative treatment which may markedly improve the patient’s quality of life and avoid the onset of irreversible damage to the median nerve. There is no universally accepted treatment for CTS. Surgical division of the transverse ligament is generally preferred for patients with severe symptoms, hypertrophy of the thenar eminence or marked EMG abnormalities whereas conservative management is usually adopted in patients with mild to moderate symptoms.

The recognition and elimination of factors likely to increase pressure on the carpal tunnel are essential in the management of CTS. Wrist-hand appliances are advisable to limit flexion-extension movements and decrease the pressure within the channel. The most effective appliances block the wrist in a neutral position rather than in extension, and those with rigid palm inserts are recommended. Appliances are more effective if they are used within three months after the onset of symptoms and worn day and night. Ergonomic computer keyboards and mouse pads should be used. Non conventional treatment based on yoga strengthening and stretching exercises for the arm have proved more effective than appliances.

The following medical treatments have been used to improve the symptoms and evolution of CTS:

**Local steroid injections.** Dammers provided convincing evidence that a single injection of methylprednisolone proximal to the carpal tunnel significantly improves symptoms even in the long-term (one year), without giving rise to major side effects or complications. Steroid injection will attenuate symptoms in more than 75% of cases and is associated with an improvement in median nerve conduction velocity. Methylprednisolone administered at a dose of 15 mg proved effective, with clinical remission lasting up to eight to 12 months, but percentages varied widely after 12 months (20-92%). Factors associated with recurrence include major EMG abnormalities, impaired sensitivity, persistent paraesthesia, and weakness or hypertrophy of the thenar eminence.

**Vitamin B6.** Two trials versus placebo failed to demonstrate the utility of this vitamin supplement.

**Oral NSAIDs, diuretics and steroids.** Few studies have investigated these drugs versus placebo or other treatments. One study compared four groups (placebo, diuretics for four weeks; NSAIDs for four weeks; prednisolone 20 mg for two weeks followed by 10 mg for two weeks) showed that NSAIDs and diuretics were not more effective than placebo and less effective than oral steroids.

**Ultrasound (US).** Two trials have been published on the use of ultrasound versus “placebo” physical therapy (application of the probe with zero US intensity). The first trial on 18 women yielded negative results (but the strength of the study was poor: only 18 patients). The second trial on a larger number of patients (45) published in the BMJ demonstrated a favourable outcome after US both on symptoms and EMG findings. However, patients underwent 20 sessions, ten daily and another ten twice weekly for another five weeks.

Other treatments include studies on magnetotherapy, acupuncture, muscle exercises and chiropractics failed to demonstrate any benefit on symptoms compared with placebo.

**Surgery** resolves CTS in 70% of cases with clinical remission lasting up to 30 months. Rare but sometimes severe complications may arise (accidental nerve injury, post-operative infection). Recurrence is not uncommon, especially when CTS is secondary to diabetes, myeloma or amyloid disease.

O₂-O₃ treatment is limited to few literature reports, precluding comparison with studies on other treatment options. However, the clinical results reported in this study are extremely encouraging and comparable to those of the most widespread conservative treatment, i.e. a single injection of methylprednisolone. Compared to steroid injection O₂-O₃ infiltration seems to guarantee stable improvement of symptoms up to one year after treatment and its efficacy was confirmed at two year follow-up in 20 patients (94%).

O₂-O₃ treatment is based on three main mechanisms of action shared by the treatment of herniated disc in the spine:

a. indirect vessel-mediated mechanical decompression of the nerve roots by increasing intra and trans-tissue oxygenation with reduced hypoxia and venous and lymphatic stasis.
b. *action on the cell-mediated inflammatory response* both by inhibiting the release of proteinase by macrophages and polymorphonucleates and by increasing immunosuppressive cytokines (interleukin 10, TGF-beta) 23.

c. *action on the biohumoral inflammatory response*, inhibiting the release of prostaglandins and pro-inflammatory bradykinins 24.

Our study showed a good response of pain to O2-O3 treatment. 90% of treated hands showed a significant improvement in symptoms after O2-O3 injection. In addition, improvement remained stable in the long-term: at one year follow-up 70% of patients no longer had symptoms while 17% had a good control of symptoms. Further studies will establish whether symptoms remain the same in the long-term (two years or more), and whether synergy with other treatments will further reduce the percentage of cases referred for surgery. Before O2-O3 treatment CTS patients should be informed of the different therapies available. Symptoms and EMG findings must confirm the diagnostic suspicion and rule out severe forms of CTS not amenable to conservative management. Patients must be advised that therapeutic benefit will appear two to three weeks after treatment. Once the diagnostic boundaries of CTS and the patient’s expectations have been defined, O2-O3 treatment has a high success rate without significant side effects.

References

Indications and Limits of Intra-articular Oxygen-Ozone Therapy for Rotator Cuff Tendinopathy

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Key words: tendon, rotator cuff, infiltration, ozone, outcome

SUMMARY - A number of reports have described the treatment of painful shoulder conditions using an oxygen-ozone gas mixture. For prolonged efficacy, the indications for this treatment must be restricted to selected well documented disorders.

Introduction

Given its well-known properties, oxygen-ozone has been used to treat musculoskeletal disease in many joints and articular disease involving the cartilage, tendons and meniscocapsular injury. With a few rare exceptions, the success of this treatment is not confined to resolving pain which is only a by-product of inflammatory or degenerative disease resulting from microtrauma or of unknown origin. If this were the case, the underlying disease could be underestimated, thereby delaying surgical treatment and exacerbating the condition. Thanks to major advances, current diagnostic imaging techniques allow accurate clinical classification which is essential for a long-term outcome. Interesting developments have occurred in the treatment of the shoulder, or glenohumeral, joint. Despite its anatomofunctional complexity, this joint lends itself to treatment by ozone injection because disorders affecting the rotator cuff tendons are common in the elderly with fewer associated severe chondral disease such as that involving the leg (hip, knee and ankle) caused by daily weight-bearing and gravitational stress.

Materials and Methods

Patients with painful shoulder conditions must be correctly diagnosed by thorough clinical examination and history-taking. A knowledge of special shoulder tests is essential together with routine imaging including:

1) Conventional x-ray: frontal views (A-P) completed by radiograms in internal, external and lateral rotation, outlet view (lateral view of the scapula inclined 10°), sometimes associated with further specific views to disclose possible:
   - Acromioclavicular osteophytes (figure 1).
   - Advanced arthrosis.
   - Large tendinous calcifications.
   - Previous Hill-Sachs or Bankart traumatic bone lesions.

   These elements constitute relative contraindications to treatment as they are signs of joint laxity or advanced involutive-degenerative changes not amenable to oxygen-ozone therapy.

2) Soft tissue examination:
   a) Despite being an inexpensive test, ultrasound is operator dependent requiring a sound knowledge of normal anatomical ultrasound findings and will not distinguish more advanced tendinous changes from partial or complete rupture.
   b) In addition to evaluating cuff lesions, MR scan will classify the degree of tendinosis (see Goutalier’s classification); abundant fat deposition in the tendon would deprive ozone of its oxygenating effects and eutrophying potential.

   Other examinations such as CT scan and arthrography will only be required if diagnostic doubts persist. The ideal candidates for oxygen-ozone
Figure 1  Acromioclavicular osteophytes.

Figure 2  Physiological acromial arch.

Figure 3  Oblique axial scan.

Figure 4  No fat deposition in the muscle.

Figure 5  Partial insertional lesion of the supraspinatus tendon.
infiltration are patients aged between 40 and 65 years with tendon disease of the supra-subspinatus insertion and/or long head of the biceps.

In theory candidates would include overhead workers (those raising objects above the head) or tennis and volleyball players who could partially correct the movements triggering injury or a concomitant inflammatory process treated with NSAIDs or other medication without pain relief and with limitation of shoulder movement (see figures 2-5).

Oxygen-ozone infiltration is performed with the patient in a sitting position via posterior intra-articular access (known as the “soft spot” in arthroscopic surgery around 1.5 cm medially and inferiorly to the posterolateral angle of the acromion) or lateral. With this approach it is more difficult to reach the genohumeral joint so the ozone is injected into the subacromial space affected by bursitis with a direct effect of ozone on the rotator cuff.

A 20 G needle is usually used moving to a 22 G 88 mm spinal needle in patients with more developed muscular trophism to ensure injection into the space desired.

The volume of \( \text{O}_2-\text{O}_3 \) infiltrated is 10 ml at a concentration of 10 \( \mu \)g/ml.

The imaging-guided technique described by other authors \(^2\) is not deemed necessary if the procedure is performed by experts in the shoulder joint.

No additional drugs or anaesthetic, administered in association by others in more severe cases \(^3\) are given to our patients either locally or systemically. The treatment schedule includes five injections at weekly intervals accompanied by a passive rehabilitation programme with a physiotherapist and self-administered exercises (see drawing 1) to facilitate joint recovery and maintenance of the outcome achieved (usually after two months), to strengthen the extrarotator muscles.

**Results**

The following criteria were applied in 14 patients (eight women, six men, average age 53 years) at two year follow-up. The Visual Analogue Scale (VAS) and Constant and DASH\(^1\) scales were used to evaluate patient outcomes.

The VAS scale dropped from an average of 8.5 to an average of 3 at one month follow-up to an average 1.5 after two months which remained constant over time. At long-term follow-up the Constant and DASH scales documented residual pain in 15% of patients, limited movement in 10% and loss of strength in 20%.

**Discussion**

Oxygen-ozone infiltration resolved shoulder pain in a high percentage of our patients. It is a low cost treatment without major complications. However, the indications for treatment must follow accurate diagnostic classification, not only to ensure a successful outcome but also to avoid pointless lowering of the pain threshold in cases of ingravescent degenerative disease. A disappearance of pain may not necessarily be the prime aim of treatment. For years the treatment for disease known as “scapulohumeral periarthritis” was steroid injection with the risk of further damage to already injured tissues. Current clinical knowledge and information provided by diagnostic imaging techniques will avoid inappropriate use of the infiltration technique. The following issues remain open in relation to medical ozone injection:

1) The efficacy of ozone therapy in cases of calcified tendinitis of the cuff both in the precalcified stage (fibrocartilaginous metaplasia) and in the calcified stage, possibly in association with well established successful methods like shockwave therapy \(^4\) to enhance the reparative effect of ozone.

2) Is the distension capacity of the ozone gas mixture an important or determinant mechanical effect (as it acts on the capsular and bursal adherences)? Unlike those already undertaken on painful shoulder \(^5\) no double blind studies have been carried out only with air administration.

3) The capacity of oxygen-ozone as an adjunct therapy in the recovery of the anatomo-histological features of tendon after surgery for disease involving the rotator cuff directly (complete lesions) or secondarily (acromial osteophytes).
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Ozone Treatment of Lower Limb Trophic Ulcers

A Case Report

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Key words: wounds, ozone bag, reepithelialization

SUMMARY - This paper describes the management of a patient with two trophic ulcers on the distal part of one leg using ozone administered to the treatment area through a sealed plastic ozone bag. A series of treatment sessions over a period of six months without adjuvant treatment led to a disappearance of one of the ulcers and subcomplete remission of the other. Concomitant ozonized autohaemotherapy was avoided in our patient due to a hereditary coagulopathy. The treatment technique and patient outcome are discussed.

Introduction

Ozone has well known disinfectant and trophic effects and has been administered in different ways to treat trophic ulcers caused by various diseases.

Clinical findings in chronic ulcerative lesions usually include four key features encountered to varying degrees:

- Devitalized or necrotic tissue.
- Infection.
- Impaired fluid balance.
- Inadequate epidermal regrowth.

As a result, treatment aims to remove the necrotic tissue, combat inflammation and infection, modulate exudation and stimulate reepithelialization. Ozone can carry out all these tasks except for removal of devitalized or necrotic tissue which is done by surgical, mechanical or enzymatic procedures.

Infection: the disinfectant action of ozone is second only to that of iodine with bactericide, viroicide and fungicide effects. Impaired fluid balance: ozone favours the resorption of oedema and decreased tissue acidity. Inadequate epidermal regrowth: vasodilation, hyperoxygenation, decreased tissue pH, and fluid resorption stimulate metabolic activation with cell proliferation. Cytokines increase, namely TGF-β1 with an increase in platelet aggregation. In particular, KGF, FGF and EGF are activated resulting in endothelial repair and new production of essential hyaluronic acid, and new formation of collagens III and I, stimulating reepithelialization.

Materials and Methods

This case report concerns a 69-year-old woman with two skin ulcers on the medial side of her left leg, cranial to the malleolus. Her independence was strongly reduced due to her limited ability to walk and generally move her left leg. In addition her socialization was limited by her being ashamed to be seen in public and fear of even mild injury. History-taking disclosed a hereditary coagulopathy (Antithrombin III deficiency). On clinical examination the two ulcerated areas differed in size, shape and severity but both presented necrotic tissue, exudates and an inflammatory ring. The patient underwent a series of topical treatments with local administration of oxygen ozone. The O₂-O₃ gas mixture was administered through a hard (glass or plastic) or soft (polyethylene or similar) bag for health use. Because of her coagulopathy, ozonized autohaemotransfusion was avoided.

The following equipment was used:

- An Alnitec Ozo Futura 2 ozone generator fitted with an aspiration pump, an ozone concentration detection device and entry and exit tubes for the ozone chamber.
- A cylinder of O₂ for medical use.
- Sterile saline solution.
- Polyethylene bags to construct the ozone chamber.

After debridement of the necrotic tissue and washing the ulcerated area with sterile saline solution, the ulcer was kept moist with a wet sterile gauze in situ as ozone only acts after being dissolved in saline solution. The ozone chamber was...
then constructed to contain the O₃ treatment area. The patient’s left foot was placed in the closed end of the bag, the plastic tube of entry of the gas mixture was fixed close to the largest wound, while the exit tube was fixed more cranially. The bag was fixed in place by a Velcro strap beneath the knee. A vacuum was created in the bag by aspirating the air within it and insufflating an O₂-O₃ gas mixture at an ozone concentration of 35 mcg/ml, until the bag was completely distended. Having suspended entry flow, the mixture was left to act for 30 min. A sterile medication was then applied and the patient discharged. This procedure was repeated twice weekly for the first three months, then weekly for another two months and lastly every two weeks for one month. Digital images of the two ulcers were taken during the treatment sessions to document lesion evolution (figure 2). No other topical treatment was administered throughout the period of ozone management. The progressive favourable results in terms of ulcer extension, inflammation/infection, progress of reepithelialization motivated the patient and operator to continue with the treatments.

Discussion and Conclusions

Our patient’s coagulopathy forced us to limit treatment to topical application of O₂-O₃ alone without autohaemotransfusion to avoid skin injection. We are aware that this obviated the synergic action of concomitant ozonized autohaemotherapy ¹. Despite this, our patient had a positive outcome and results have remained stable two months after the end of treatment. Topical administration of an oxygen ozone gas mixture can be deemed a valid treatment for trophic ulcers.

References


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Safety of Topical OLEOZON® in the Treatment of Tinea Pedis: Phase IV Clinical Trial


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Key words: ozonized vegetable oils, phase IV clinical trial, safety, tinea pedis, adverse drug reactions, Oleozon®

SUMMARY - The efficacy of topical OLEOZON® against tinea pedis has already been demonstrated. The aim of the present study was to assess the adverse reactions associated with topical OLEOZON® in patients with tinea pedis. A multicenter, open, phase IV clinical trial was carried out. An adverse drug reaction report form specifying the reactions most commonly associated with topical OLEOZON® was designed. This study lasted three years. Patients were treated with topical OLEOZON® twice a day for six weeks. Of the total of 2596 patients admitted to the study, 2165 (83.4%) patients finished the treatment. The main cause of drop out of the 431 patients (16.6 %), was the scant attendance at the clinical evaluation. Six patients (0.3%) showed adverse reactions. The most frequently reported adverse reactions were skin burning sensation, pruritus and erythema of mild intensity. Skin burning sensation was considered, according to the causal relationship, as definite; pruritus and erythema were considered probable. Taking into account the number of patients that finished the treatment, an efficacy of 92.7% (2007 patients cured) was achieved. The favourable safety profile achieved with topical OLEOZON® in this study, together with its demonstrated efficacy and its low cost justify the extension of this treatment in clinical practice for patients with tinea pedis, particularly in developing countries.

Introduction

Tinea pedis is a very common and often chronic foot infection caused by fungi of the genera Trichophyton, Microsporum or Epidermophyton. Topical and oral OLEOZON® (ozonized sunflower oil) is a medication produced in Cuba which has been evaluated previously in different clinical trials. It is already registered for the treatment of tinea pedis, impetigo and giardiasis. Its remarkable germicidal action has been well documented, as well as its lack of toxicity and low cost.

Topical OLEOZON® was evaluated in a controlled randomized phase III assay, using ketoconazole (Nizoral®) as the comparing group. The results demonstrated that no significant differences were found between the two medications, nor were any side-effects or bacterial superinfection observed in the study.

Adequate safety profiles for tinea pedis treatment were observed in different clinical trials, as for topical OLEOZON®. However, it was not known whether a similar profile would be found in routine clinical practice conditions using a large number of patients. Therefore, taking into account the characteristics of OLEOZON® and the need to find effective, low-cost safe antymycotic drugs, the aim of this study was to perform a multicenter open phase IV clinical assay to evaluate the true picture of adverse drug reactions (ADRs) and the drug’s effectiveness in routine clinical practice.

Patients and Methods

A multicenter, open, phase IV clinical assay was carried out aimed at evaluating the possible ADRs during the treatment of patients with tinea pedis using topical OLEOZON®. An ADR report form, specifying the reactions most commonly associated with OLEOZON® was designed. This study lasted three years. Four hospitals from different provinces of Cuba participated. All the patients were clinically (presence of maceration, desquamation, fissures, erythema, vesicles and/or pruritus) and mycologically (positive culture of skin scrapings of the affected areas in Sabouraud glucose agar-chloramphenicol) diagnosed as suffering from tinea...
pedis. They were aged over 15 years, of either gender and any race and without previous treatment or with more than five days without any topical or systemic medication. From the study were excluded patients with decompensated diseases, hypersensitivity to the medication and those being treated with antibiotics, corticoids, cytostatics or immunedepressant drugs.

**Treatment**

Patients were treated with topical OLEOZON® (each 100 ml contains 8-12 % hydroxyperoxides of unsaturated triglycerides as active oxygen 17,18), twice per day, for six weeks.

**ADR Evaluation**

An ADR is defined as any noxious and undesired effect to a drug observed at doses usually administered therapeutically in humans. The severity of ADR was classified in four levels:
1) Mild, when the side-effect did not significantly interfere with the normal functions of the patient, no therapy was necessary;
2) Moderate, when the side-effect produced an impairment of the normal functions of the patient, without being a risk to his/her health, but needed specific treatment;
3) Severe, when the side-effect produced a significant impairment of the normal functions of the patient, without being a risk to his/her life, but hospitalization was required;
4) Very severe, if a reaction was potentially life-threatening or contributed to the patient’s death.

A qualitative assessment was used to classify the causal relationship as definite, probable, possible or doubtful 19. According to this method, a reaction was classified as definite if it (A) followed a reasonable temporal sequence after drug administration; (B) followed a known pattern of response to the suspected drug; (C) could not be explained by concurrent disease or other drugs; and (D) was confirmed by improvement upon removal of the drug and by reappearance on rechallenge. It was considered probable if it had the criteria (A), (B), (C) and was confirmed on suspension of the drug but not on rechallenge.

A reaction was defined as possible if it followed a reasonable time sequence to the application of the drug, but could also be explained by concurrent disease or other drugs.

Finally, a reaction that was more likely related to factors other than the suspected drug was classified as doubtful.

**Clinical Efficacy Evaluation**

As a second aspect of this clinical assay, the efficacy of topical OLEOZON® was measured in all the patients studied, and also with respect to the different clinical forms present in tinea pedis. The efficacy was evaluated as clinical cure (disappearance of all lesions, for that reason no mycological diagnosis was needed) before or in six weeks. If a patient was clinically cured before six weeks of treatment, the medication was continued until six weeks. If a clinical cure was not achieved at the end of the treatment, this was considered a failure.

Patients were submitted to clinical and ADR evaluation every two weeks and at the end of the study (six weeks). If any side-effects appeared in the meantime, patients would immediately inform the physician to classify the severity of ADR and to determine the causal relationship. After finishing the treatment, all patients had a follow-up at six months to check for relapse.

The study was approved by the Scientific Committee of the Ozone Research Center. As the study only involved the usual medical procedures (this is a medication already registered in Cuba for the treatment of tinea pedis, with its license to use it) and confidentiality of the subjects was maintained, ethics approval and patient informed consent were not required.

**Statistical Analysis**

Univariate analyses were performed to identify the variables that could influence ADRs. The analysis was assessed by χ2 test or Fisher’s exact test, depending on the minimum expected values. For the efficacy evaluation, data were analyzed by one-way analysis of variance (ANOVA) followed by a multiple comparison test.

**Results**

In this study, the mean value of the evolution time of the disease was 60 months with five relapses per year. The mean age was 35 years, 85% were male and 55% were white. Interdigital lesions were the most common symptom in more than 90%; the plantar lesion was present in less than 50% of cases.

A total of 2596 patients suffering from tinea pedis were included in this study, but only 2165 patients (83.4%) finished the treatment because 431 (16.6%) dropped out due to scant attendance at the clinical evaluation (every 2 weeks). Taking into account the number of patients that finished...
the topical OLEOZON® treatment, an efficacy of 92.7% (2007 patients cured) was achieved and only 7.3% (158 patients) were not cured (figure 1). However, if we consider as failure the number of patients that abandoned the treatment the effectiveness decreases to 77.3% (analysis by intention to treat). Only six patients (0.3%) presented ADRs. The most frequently reported ADRs were skin burning sensation, pruritus and erythema of mild intensity. Four patients presented skin burning sensation, one patient presented skin burning sensation and pruritus and the other one also had skin burning sensation but with erythema. Once the ADRs appeared in these six patients, the treatment was suspended for 24h. Patients were evaluated during this period to confirm their improvement upon removal of OLEOZON® and the reappearance or not of the ADRs on rechallenge. Skin burning sensation was considered definite according to the causal relationship; pruritus and erythema were considered probable. No causal relationship considered as possible or doubtful was found in this study (table 1).

Considering the number of patients that finished the treatment, a major incidence (50.1%) of the scaly form of tinea pedis, followed by the macerated form (31.9%), were present in this study. The scaly and macerated forms demonstrated a high percentage of cured patients, with 97.9 and 94.9%, respectively (table 2).

No relapses were found in six months of follow-up.
Discussion

The results of this study suggest that topical OLEOZON® is a safe drug with an excellent post-marketing safety profile. Post-marketing monitoring is an important procedure to detect reactions that can become apparent only when the drug is used in a large and varied population. Indeed, those observed in clinical trials for tinea pedis do not reflect the true behaviour of ADRs due to the limited number of patients.

Active surveillance provides a vital service to the healthcare system by identifying and assessing early warning signals, and when appropriate, taking preventive action to minimize the deleterious effects of drugs. In Cuba this has a special relevance because the information generated in clinical trials can be limited by the patients' recruitment rate.

The most frequent ADRs associated with topical OLEOZON® therapy were skin-burning sensation, pruritus and erythema. These ADRs had also been reported in the treatment of impetigo with topical OLEOZON® in a phase III clinical trial carried out in 136 children. However, some contradictions are present with respect to ADRs. In the study, no ADRs were reported with the use of topical OLEOZON® in adults with different diseases (tinea pedis, pyoderma, onycomycosis, simplex herpes). Also, another study (unpublished observations) carried out in 80 children with impetigo reported no ADRs. In this study only 0.3% of ADRs were found.

Skin burning sensation could be a consequence of topical OLEOZON® application, due to the active metabolites that are formed in the reaction of the ozone with the sunflower oil and the patient’s sensitivity. For that reason, skin burning sensation can be classified as definite, according to the causal relationship, however, erythema and pruritus were in the group of probable ADRs (confirmed on suspension of the drug but not on rechallenge).

A high efficacy (92.7%) was obtained when all the patients that finished the treatment are considered. However, with respect to the analysis by intention to treat, where all the patients included in the study are considered, the effectiveness decreased to 77.3%, similar to that obtained in the phase III clinical trial. This is an important point to take into account, since in daily practice patients sometimes interrupt treatment, this result being a truer figure of medication efficacy. The incidence in respect to the different clinical forms, is similar to that already reported, where the scaly form occupied the first on the list. Also, the scaly form responds best to different treatments.

Another aspect to highlight is that topical OLEOZON® exhibits an antifungal and antibacterial activity as well as an anti-inflammatory property. Normally, the severity of tinea pedis infection determines the course of treatment required. Mild infections may be resolved using a topical agent, but are commonly associated with high relapse rates. However, more severe cases (eg, dermatophytosis complex) may require oral and topical treatment that eliminates the bacterial and fungal infection and sometimes if inflammation is present an agent with a known anti-inflammatory action may be needed. All these drugs can be accompanied by side-effects such as gastrointestinal distress, headache, and hepatic toxicity, among others. In our study, the mean value of the evolution time of the disease was 60 months with five relapses per year, then, we can consider that we are studying chronic patients. This six weeks topical OLEOZON® treatment guaranteed the absence of relapses (at least in the six months of follow-up), and the presence of superinfection due to bacteria and the associated inflammation. In this case OLEOZON® will be the best choice due to its germicidal and anti-inflammatory properties, its low cost, safety and tolerability (favourable cost/benefit ratio).

Conclusions

The favourable safety profile achieved with topical OLEOZON® in this study together with its demonstrated efficacy and low cost justify the extension of this treatment in clinical practice for patients with tinea pedis, particularly in developing countries.

Acknowledgements

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Sjögren Syndrome Treated with Ozone Therapy

A Case Report

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Key words: Sjögren syndrome, dry syndrome, autoinmune disease, immunomodulation, hidrocolontherapy plus rectal ozone

SUMMARY - Due to its immune modulation effect, ozone therapy shows high efficacy in the treatment of autoimmune dysfunctions like Sjögren syndrome. The patient described in this report improved her quality of life without taking strong drugs with secondary effects.

Introduction

Sjögren syndrome or “dry syndrome” is an autoimmune disease, as Swedish ophthalmologist Dr Henrik Sjögren defined it in 1930. The Sjögren syndrome combines dry eyes, dry mouth, dry skin, dry mucous membranes and dry joints and another disease of the connective tissues most commonly rheumatoid arthritis.

Diagnosis is characterized by the abnormal production of extra antibodies in the blood, antinuclear antibody test (ANA) and a Shirmer test that tests the amount of tears. The disease includes primary Sjögren syndrome and secondary Sjögren syndrome, associated with a connective tissue disease such as rheumatoid arthritis, systemic lupus erythematosus, or scleroderma.

Regular treatment for the condition comprises: artificial tears, hydroxychloroquine 200 mg/day and omeprazol 20mg/day-100mgr./day. Complementary treatment includes: AINES, cortisone derivates, antibiotics (bronchitis) and antitoxics (azatoprine and cyclophosphamide)

Patient: Female, 51-year-old. Works as a nurse in the hospital

Anamnesis: After a trip to Rome in 2001, the patient suffered an intense pain in the lumbosacral region, experiencing cramp in the legs, abdominal distension and weight loss (about 13 kg). After several clinical tests she was diagnosed with the primary Sjögren syndrome with glandular disorder and xerophthalmia.

Psychological profile: At work she has problems due to confrontation with another co worker. She had to be attended by psychologists because she felt scorn of others.

Spine: Severe lumbosacral pain in the spine worsening with movement.

Abdomen: Alter radiopaque enema examination we observed mega sigma-colon, including the cecal part. The patient had difficulty digesting vegetables feeling a sensation of abdominal distension, colic and retarded defecation.

Rectum: Weekly defecation with no sense of emptiness. The same sensation with urine function. Neurological diagnosis was constipation due to neurological dysynergy (myeloradiculitis) of abdominal walls and pelvic floor.

Respiratory system: Acute larygo-tracheo-bronchitis with dry cough and loss of voice. Lung CT scan disclosed a nodule in the apical part suspicious of TBC.

Genital system: Copious regular menses. Intermittent vaginal discharges. Vaginal dryness (needs to use a gel for coital function). Menopausal symptoms: hot flushes.

Joint bones: migratory joint pain (elbow, wrist, hip), bursitis and monoarthritis.

Skin: Dryness of skin and mucous membranes, lately with a vesicular eruption on her face.

Mouth: Periodontitis, ulcers and fissures due the lack of salivary fluid.

Blood Level Tests

Anti-cytomegalovirus antibody: 2.64 (1,10)
Anti Epstein -Barr antibody: 3.60 (1,10)
Negative for TBC (Mantoux and culture)
Zinc serum test: 59 nanogr/dL (60-150)
Retinol serum test: 0.34 nanogr/dL (0.35-0.75)
Ammonia plasma test: 64.2 nanogr/dL (10-47)

Oligoelements Blood Test (CEIA)
- Deficiency-descending order: aluminium, molybdenum, copper, iron, rubidium, nickel, silicium, lead, manganese, cobalt and selenium.

Aminoacids Serum Test
- Taurine serum test: 77 (80-217)
- Tryptophan, and threonine were normal.
- Levels of lead, mercury, homocysteine, cadmium, chromium, selenium, magnesium, vitamin B6 (pyridoxal phosphate) were normal.

Microscopic study of fresh blood drop showed:
- Sludge of red cells (grade 2/3) suggesting deficiency and enzymatic oxidation and high oxidation.
- Many lipid chains (altered lipid metabolism).
- Blocks of proteins related to a lack of pancreatic enzymes and intestinal malabsorption.
- Candidiasis (degree 2) related to immune system impairment.
- Peroxide lipids (degree 2) related oxidative stress.
- Bacteria (degree 2) signifying high intestinal permeability.
- Uric acid.

Brain Magnetic Resonance Scan
- Discrete cerebral atrophy
- Hyperintensity focus in radial aspect suggesting hypoxic-ischemic chronic areas.

Diagnosis hypothesis: Hemorrhagic infarct in the left zone of the brain.

Ozone Therapy

We started the treatment with coffee colonics and after that she received insufflations of 300 cc, 20 microgr/ml of ozone gas when the bowel seemed
to be clean. She received one session weekly for a month.

At the same time the patient was taking pre and probiotics to nourish bacterial flora. She also changed her diet including more fruits and cereals (fiber) and nutrients such as zinc, retinol and tryptophan, because values were low in serum.

After the second week she received autohemotherapy (100 cc-50 microgr/ml) twice a week.

**Evolution of the Patient**

The patient is currently re-established after three months of treatment. All blood levels have normalized except anti-cytomegalovirus antibody and anti Epstein–Barr antibody that have also improved. She is working (as a nurse) and does not need to take any regular drugs prescribed by her rheumatologist.

The microscopic morphology of the blood has improved. The worst problem she has is the bronchitis, but it is controlled with an extra session of autohemotherapy major + ozonized autoserum with intramuscular and homeopathic drugs too (Oscillococcinum 200 K, Bryonia and Stannum).

In conclusion, Ozone Therapy has proved useful in this uncontrolled group of autoimmune diseases.
The Term “Liquid Polyatomic Oxygen” Requires a Correction but Chemo- and Radiotherapy Combined with Ozone Therapy May Help Cancer Patients

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Key words: water-soluble oxygen-ozone, ozonetherapy, chemotherapy, radiotherapy, oxidative stress

SUMMARY - Recently, the terms of “ossigeno poliatomico liquido, OPL” (liquid polyatomic oxygen) and “ozono in forma liquida” (ozone in liquid form) have been used but they require a correction because intravenous (IV) injection of oxygen and ozone in the liquid state will freeze the blood and kill the patient. It is suggested the correct term “water-soluble oxygen-ozone mixture” (ossigeno-ozono idrosolubili) be used because this erroneous concept may increase the ostracism towards ozone therapy. On the other hand, we have long favoured the combination of ozone therapy with chemo- and radiotherapy to enhance the cytotoxic effects of oxidizing compounds against cancer cells.

Introduction

Two papers have been recently published using improper terms (namely, “ossigeno poliatomico liquido, OPL” and “ozono in forma liquida”) to describe the infusion of water-soluble ozone via a central venous catheter with the help of either a pump or an elastomer in cancer patients 1,2.

To our knowledge the term of polyatomic oxygen has been used since the 1920s 3 to mean that under an electric discharge oxygen can generate about 5% ozone (O₃) measurable at 253.7 nm, and less than 1% of oxygen 4 (O₄, monitored at 151.1 nm). Traces of multiple molecular structures up to oxygen₆₄ (O₆₄ and greater) were also postulated by Basil. E. Wainwright 4. While ozone is relatively stable (t₁/₂ = 40 min, at 20°C), all the other polymeric oxygen molecules decompose immediately. O₄, the tetra-atomic molecule, also breaks down almost instantaneously into singlet oxygen atoms releasing eight-plus free radical electrons in the process 5. This clarifies that ozone is the crucial molecule and the term polyatomic oxygen has been used since the 1920s 1 to mean that under an electric discharge oxygen can generate about 5% ozone (O₃) measurable at 253.7 nm, and less than 1% of oxygen 4 (O₄, monitored at 151.1 nm). Traces of multiple molecular structures up to oxygen₆₄ (O₆₄ and greater) were also postulated by Basil. E. Wainwright 4. While ozone is relatively stable (t₁/₂ = 40 min, at 20°C), all the other polymeric oxygen molecules decompose immediately. O₄, the tetra-atomic molecule, also breaks down almost instantaneously into singlet oxygen atoms releasing eight-plus free radical electrons in the process 5. This clarifies that ozone is the crucial molecule and the term polyatomic oxygen was used as a camouflage to avoid irritating the Food and Drug Administration. Eventually, the term “oxygen in its molecular forms” 6 was also included in a proposal to the Italian Parliament for possible permission to administer polyatomic oxygen to patients 6. As the proposal will be evaluated by the National Council of Health, it looks probable that some expert advisers will reject the proposal. Nonetheless, on the basis of the FDA investigation regarding the misuse of ozone, Wainwright was sentenced to 37 months’ imprisonment.

The aim of this brief annotation is to point out the futility of erroneous terms and to explain that the correct use of ozone as a pre-drug may enhance the efficacy of chemo- and radiotherapy in cancer patients.

Discussion of the Problem

We would like to bring to the attention of the ozone therapists that the term “liquid polyatomic oxygen” is wrong because firstly, liquid oxygen is used only as a rocket-propellant under stringent conditions and secondly, ozone in the liquid state is highly explosive and exists at ordinary pressure conditions only below –111.9°C. Liquid ozone certainly cannot be used in medicine because it literally will freeze the blood leading to heart arrest. On the other hand, it is well known that both oxygen and ozone are physically soluble in pure bidistilled water, exactly in the amount of either 4.89 ml or 49.4 ml in 100 ml of water, at 0°C, respectively 7,8. When the gas mixture composed of oxygen (95%) and ozone (5%) is bubbled in pure water, ozone, in relation to its relative pressure, temperature and solubility coefficient, will dissolve as a gas in the
water and will saturate it within five minutes up to 26%\(^9\). However half of the ozone dose, even if kept in a tightly-closed ozone-resistant container will spontaneously decompose to oxygen during the following 11 hours at 20°C. If the container is worn by a patient at about 30°C, ozone decays rapidly and the half-life is about 2.5 hours. Thus, provided that the gas mixture is dissolved in pure water at 760 mm Hg, it is possible to infuse water-dissolved oxygen and ozone VERY SLOWLY into the blood circulation. To the best of our knowledge, this technique has been used by Belianin since 2000 to decrease the resistance of multiresistant mycobacteria in TBC patients\(^{10}\). In our opinion, this is only another technique for ozone administration that is less dangerous than the direct IV administration of gas that was correctly prohibited owing to serious side effects and the risk of oxygen embolism. Then it should be obvious why the infusion of “liquid polyatomic oxygen” will catastrophically freeze the blood and why this term should be proscribed.

The proposed technique still present several disadvantages: firstly, there is no documented proof that a continuous delivery of solubilized ozone in pure water into the central venous system is more effective than the classical, practically risk-free, infusion of blood ozonated ex-vivo into a cubital vein. In skilled hands, complications such as pneumothorax and sepsis are rare but do happen. Thrombosis is also a risk but it may be controlled by anticoagulants. Obviously the patient must be well informed about the implantation procedure, agree to the procedure and sign an informed consent form. The system can run smoothly only if the ozone therapist procures the daily infusions, checks the pump programming, trains the patient and assiduously checks the safety of the system. Another crucial objection is that so far the usefulness of solubilized ozone infusion without the integration of temozolomide has not been demonstrated\(^{11}\).

Although the direct (IV) injection of water-soluble oxygen and ozone is a very unusual and peculiar method of ozone administration, it deserves to be theoretically evaluated. In order to prevent pathological haemolysis (at the tip of the catheter, local hypotonicity cannot be lower than 100 mM NaCl) and considering that cancer patients undergo chronic oxidative stress, we cannot infuse more than 400-800 ml (depending upon the body weight) of pure water during 24 hours. In other words, water can be cautiously infused at a rate of 0.275-0.555 ml/min. By using the currently available ozone generators, 800 ml of water at 20°C may dissolve no more than 39.2 ml of oxygen, corresponding to about 2 mg of oxygen, and 20.8 mg ozone. However, as ozone decomposes rapidly at about 30°C, it is likely that, at best, we can deliver a negligible amount of oxygen and no more then about 5.0 µg/ml ozone per minute. Thus the daily dose of ozone may be about 7.2 mg that is below the average dose of 8.0 mg administered by ozonating 200 ml of blood ex vivo with an equal volume of gas containing 40.0 µg/ml ozone. In spite of not taking into account the different pharmacokinetic distribution of the several compounds generated by ozone in blood, this reasoning questions the validity and usefulness of the direct infusion of water-soluble ozone.

Finally the problem of complementing chemo- and radiotherapy with ozone therapy has already been extensively discussed\(^{12,13}\). The findings that different neoplastic cell types are killed by ozone in vitro are true but are worthless because water-soluble ozone will never reach the tumour environment in vivo. In fact we know only too well that once ozone dissolves in the plasma it reacts instantaneously with several biomolecules and disappears. Thus, it is illusory to hope that water-dissolved ozone will directly kill neoplastic cells in a patient. We have reported that a cycle of ozone therapy in colorectal terminal cancer patients with extensive metastases may temporarily relieve fatigue but it has no effect on tumour progression\(^{14}\). This failure is the result of the palliative chemotherapy previously performed for one to two years that not only was unable to block tumour expansion but markedly depressed vital functions. It is well known that most of the neoplastic cell types take advantage of aerobic glycolysis, “the Warburg effect” and thrive in hypoxic and acid environments\(^{12,13}\). Whenever possible, after surgical removal of the primary tumour, a correct approach would immediately combine both chemo- and/or radiotherapy with ozone therapy because the effect of radiation and cytotoxic drugs will be enhanced by ozone therapy and may eradicate residual cells. Unfortunately oncologists are antagonistic and appropriate clinical trials have not been permitted. Moreover ozone therapy is not a fashionable approach and it is disregarded. This is very unfortunate because the classical ozonated autotherapy, which is a simple, atoxic and inexpensive procedure, not only increases the oxygen level in hypoxic areas, thus decreasing neo-angiogenesis, but it also exerts useful biological effects.
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Osteoarthritis of the Hip Treated by Intra-Articular Infiltration of Oxygen-Ozone and Hyaluronic Acid (Hyalubrix®)

Preliminary results

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Key words: Osteoarthritis, hip, hyaluronic acid, oxygen-ozone

SUMMARY - Osteoarthritis of the hip is a chronic invalidating degenerative disease with high social and healthcare costs. Our study aimed to assess the therapeutic efficacy of intra-articular injection of a combination of oxygen-ozone and hyaluronic acid to treat osteoarthritis of the hip joint. Between May 2007 and January 2008, ten patients with clinical and radiological evidence of osteoarthritis of the hip were treated by intra-articular injection of a combination of oxygen ozone gas mixture and hyaluronic acid (HYALUBRIX). One month after the end of treatment all patients had a 30% recovery of function in the hip joint treated. All patients referred major pain relief reaching almost zero on the VAS scale after intra-articular injection of oxygen-ozone and hyaluronic acid. Although our series is small, the preliminary findings are encouraging. Intra-articular injection of a combination of oxygen-ozone and hyaluronic acid in the “HYALUBRIX” solution yielded prompt relief of pain and clinical symptoms in the patients treated, thereby delaying or avoiding recourse to hip replacement surgery.

Introduction

Osteoarthritis of the hip is a chronic invalidating degenerative disease with high social and healthcare costs. Its incidence is the same in both sexes affecting between 15 and 22% of the population over 55 years with a prevalence in Italy of 7.5%.

The synovial fluid in joints affected by osteoarthritis is more diluted and less viscous as its polysaccharide hyaluronic acid concentration is reduced with a decrease in molecular size and capacity for molecular interaction.

The American College of Reumatology recognizes viscosupplementation as a valid treatment for osteoarthritis.

Intra-articular injection of hyaluronate tends to re-establish the physiological properties of the synovial fluid with a recovery of the pharmacological functions of hyaluronic acid.

Systematic reviews of the literature show that intra-articular injection of hyaluronic acid decreases pain and improves joint function in a large number of patients.

In addition, many uncontrolled observational studies indicate that the outcome of treatment lasts for several years.

Another consolidated mini-invasive treatment for both primary and secondary forms of arthritis is intra and peri-articular injection of an oxygen-ozone gas mixture (O₂-O₃)³⁴.

Aim of the Study

Our study aimed to assess the therapeutic efficacy of intra-articular injection of a combination of oxygen-ozone and hyaluronic acid to treat osteoarthritis of the hip joint.

Materials and Methods

Between May 2007 and January 2008, ten patients with clinical and radiological evidence of osteoarthritis of the hip were treated by intra-articular injection of a combination of oxygen ozone gas mixture and hyaluronic acid (HYALUBRIX). Patients were aged between 43 and 65 years. Osteoarthritis was primary in nine patients and post-traumatic in one.

A number of actions were taken before treatment including: weight loss, respiratory exercises...
with a cycle of functional movement re-education, physical therapy and physiotherapy counselling, stretching and joint exercises, assessment of pain using the VAS scale and hip joint motion measuring degrees of flexion and abduction.

Each treatment session consisted in an intra-articular injection of 8-10 ml of an O₂-O₃ gas mixture as a concentration of 27 mcg/ml, followed by an intra-articular injection of the “HYALUBRIX” viscoelastic solution using a prefilled disposable syringe containing 30 mg/2 ml of hyaluronic acid sodium salt.

The treatment cycle comprised five successive weekly injections performed via a lateral approach under radioscopic guidance using a 75 mm BD spinal needle 22 GA (figures 1-8). Patients were
instructed to rest and use ice therapy after each treatment session.

Outcome was assessed one month after the end of the therapeutic cycle by clinical examination performed by the same physician who had monitored the patient prior to treatment using the Womac Index assessing pain, stiffness and joint function.

Results

One month after the end of treatment all patients had a 30% recovery of function in the hip joint treated. All patients referred major pain relief reaching almost zero on the VAS scale after intra-articular injection of oxygen-ozone and hyaluronic acid.
Discussion

The theory underlying treatment of osteoarthritis of the hip joint by intra-articular injection of oxygen-ozone and hyaluronic acid is based on combining the properties of hyaluronic acid with oxygen-ozone. Hyaluronic acid serves to rebalance the synovial fluid, while the oxygen-ozone gas mixture is known to have anti-inflammatory, analgesic and eutrophic effects and stimulates the formation of new blood vessels. The “HYALUBRIX” viscoelastic solution we used contains a hyaluronic acid sodium salt obtained by bacterial fermentation from a high molecular weight fraction (> 1500 kDa) at a high concentration (1.5%). Its strong resistance to intra-articular metabolism means that the solution is biocompatible and can be administered in repeated doses. Our patients showed two distinct phases in the overall therapeutic outcome supporting the theoretical basis of the treatment. The first involved pain relief with a functional recovery of hip motion; the second was characterized by a disappearance of pain, recovery of gait and postural joint loading. Radioscopic guidance ensured accurate intra-articular insertion of the needle thereby avoiding the risk of injecting the hyaluronic acid outside the hip joint. Another advantage of radioscopic guidance is that it offered objective documentation of the treatment procedure in each patient. Despite literature reports of a pseudo-inflammatory local reaction, no complications were encountered in any of our patients. The only adverse effect reported was an intense pain and limitation of joint motion on the day after injection which fully resolved within the following 24 hours. No infectious complications occurred in our cohort since regular sterilization procedures and the antibacterial action of ozone limit the risk of infection of a deep joint like the hip. Although our series is small, the preliminary findings are encouraging. Intra-articular injection of a combination of oxygen-ozone and hyaluronic acid in the “HYALUBRIX” solution yielded prompt relief of pain and clinical symptoms in the patients treated, thereby delaying or avoiding recourse to hip replacement surgery.

References


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Obituary of the Prof. Francantonio Berté
In Memoriam del Prof. Francantonio Berté

It is with great sorrow that we write these words in memory of the late Professor Francantonio Bertè. His passing has deeply affected everyone in the oxygen-ozone therapy world for it was largely thanks to his commitment that ozone therapy is today a recognized scientific therapy.

We would like to recall for our readers the broad spectrum of activities conducted by Professor Bertè during his distinguished career as an academic and scientist.

Born in Milan on 29th June 1932, Professor Bertè graduated in pharmacology and medicine from the University of Pavia, subsequently becoming a lecturer at the Pavia Faculty of Medicine in 1976.

From 1973 to 2004, he headed the Specialization School of Medical Hydrology, while from 1973 to 1998 he also directed the Institute of Pharmacology II. From 1999 to 2004, Professor Bertè was in charge of the Pharmacology, Cell and Molecular Toxicology Section of the Internal Medicine and Medical Therapy Department of Pavia University’s Medical Faculty.

Francantonio Bertè held numerous other positions during his long career, among them the presi-

E’ con profonda tristezza che scriviamo queste parole in ricordo del Prof. Francantonio Bertè la cui scomparsa ha lasciato un vuoto anche nel mondo dell’Ossigeno-Ozonoterapia; si deve infatti anche al suo impegno se questa metodica terapeutica ha oggi raggiunto una sua dignità scientifica. Ci piace ricordare in questa circostanza la figura del Prof. Bertè sotto i diversi aspetti che hanno caratterizzato la sua lunga carriera accademica e scientifica.

Nato a Milano il 29 giugno 1932, si è laureato nell’Università degli Studi di Pavia in Farmacia ed in Medicina e Chirurgia presso la cui Facoltà è diventato Professor Ordinario dal 1976.


Ha ricoperto svariate cariche accademiche tra cui la Presidenza del Centro Universitario Sportivo di Pavia dal 1974 al 1987 che è riuscito a portare ai vertici del canottaggio nazionale.
dency of the Pavia university sports centre, from 1974 to 1987. During this period he helped take the rowing team to national level.

From 1976, Professor Bertè was president of Opera Universitaria as well as being a member of the Pavia University Board.

His scientific stature and administrative skills led to his appointment as a member of the special commission set up to examine drug pricing policies and the committee oversaw the pricing of raw materials. Professor Bertè was also a member of the National Health Board and sat on the Joint Medical Drugs Committee.

Professor Bertè’s scientific career was no less rewarding. He worked with the Pharmacology Institute of Vienna University on correlations between cardiac and cerebral catecholamines and α and β blockers. He was also involved in numerous international university research projects on cardiopulmonary haemodynamics. Professor Bertè published more than 200 articles in national and international journals on subjects ranging from drug metabolism, bile ducts and chemo-antibiotics to the effect on cells of oxidative stress.

Alongside this work, he pursued an abiding interest in ozone-oxygen therapy. At the time still an empirically based method, ozone therapy met with wide scepticism in scientific circles. Yet Professor Bertè’s spirit of enquiry led him to become personally involved, conducting experimental research into the mechanisms of action of ozone, tolerance levels and effectiveness.

This research led to a series of clinical protocols to investigate the effects of ozone therapy on certain diseases.

Professor Bertè’s extraordinary drive was fundamental to the development and dissemination of ozone therapy, proving especially helpful during the process of obtaining ministerial approval.

His active and impassioned participation in the Ozone Therapy Consensus Conference held in Rome in September 2006 provided major inputs towards updating the treatment method. The proceedings of this conference are currently in print at the Italian National Health Institute.

For all these reasons, not least for Professor Bertè’s incredible human warmth, we now feel a deep sense of loss. We are certain, however, that his endeavours have not been in vain. Today ozone therapy enjoys scientific citizenship. It can now be conducted under strictly monitored conditions in the interests of the many patients who use and benefit from this branch of medical treatment, which, although still largely unexplored, has enormous potential.

Plinio Richelmi, Luigi Valdenassi

Dal 1976 è stato Presidente dell’Opera Universitaria e componente del Consiglio di Amministrazione dell’Università di Pavia. La sua credibilità scientifica e la capacità amministrativa lo hanno fatto chiamare come componente della Commissione per il metodo della determinazione dei prezzi delle specialità medicinali e della Commissione per l’aggiornamento del prezzario generale delle materie prime. Ha fatto inoltre parte del Consiglio Superiore di Sanità e della Commissione Unica del Farmaco. La sua attività scientifica è stata altrettanto ricca, ha collaborato con l’Istituto di Farmacologia dell’Università di Vienna studiando le correlazioni tra le catecolamine a livello cardiaco e cerebrale e le sostanze α e β bloccanti. Ha svolto inoltre diverse collaborazioni con centri universitari internazionali nell’ambito di ricerche sull’emodinamica a livello cardiopulmonare.

Ha pubblicato oltre 200 lavori su riviste nazionali ed internazionali inerenti il metabolismo dei farmaci, le vie biliari, i chemoantibiotici e gli effetti cellulari dello stress ossidativo.

In margine a quest’ultimo argomento si è sviluppato il suo interesse nel campo dell’Ossigeno-Ozonoterapia. Questa metodica era ancora allo stato empirico e circondata da scetticismo da parte del mondo accademico quando, spinto dalla curiosità intellettuale dell’uomo di scienza, ha deciso di occuparsene in prima persona. Da questo interesse iniziale sono partite ricerche sperimentali di base sui meccanismi d’azione dell’ozono e sulla sua tollerabilità ed efficacia. Grazie a queste ricerche sono stati stilati vari protocolli clinici inerenti il trattamento di alcune patologie mediante l’Ossigeno-Ozonoterapia. La forte personalità del Prof. Bertè è stata sempre presente nel corso dello sviluppo e della divulgazione di questa metodica anche per quanto riguarda gli aspetti procedurali ed amministrativi a livello ministeriale.

La partecipazione attiva ed appassionata del Prof. Bertè alla consensus conference sull’Ossigeno-Ozonoterapia a Roma nel settembre 2006 è stata essenziale per la messa a punto più attuale di questa terapia e gli atti sono in pubblicazione sui rapporti dell’Istituto Superiore di Sanità.

È per questo insieme di motivi, oltre alla mancanza della sua incredibile carica umana che possiamo dire di sentirci un po’ più soli, ma certi che l’impegno profuso dal Prof. Bertè non andrà spre- cato anche perché l’Ossigeno-Ozonoterapia potrà percorrere la strada della scientificità, all’insegna della serietà e del rigore, nell’interesse dei tanti pazienti che utilizzano e trovano giovamento e sol- lievo da questa branca della terapia medica ancora in gran parte inesplorata ma ricca di prospettive.

Plinio Richelmi, Luigi Valdenassi
SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale di Parma

Dipartimento di Sanità Pubblica
Commissione n. 35/2004

Direttore
Dr. Gianluc Ponzoni

Parma 20/3/02

OGGETTO: Attività di ossigeno ozono terapia (OOT)

Si fa seguito alla nostra precedente nota n. 45903 del 25.05.07 per trasmettere l'interpretazione del Servizio Sanità Pubblica della Regione in merito all'attività in oggetto, resa con la nota 17227 del 3.07.07.

Da tale nota, visionata dalla Commissione nella seduta dell'11 settembre 2007, si evince che l'attività stessa non è soggetta al regime autorizzatorio previsto dalla L.R. 34/98 poiché non si identifica nelle tipologie di funzioni sanitarie identificate dalla DGR 327/04.

L'attività stessa pertanto ricade sotto la diretta ed esclusiva responsabilità del medico che la effettua.

Distinti saluti

Il Presidente della Commissione
Dr. scr. Franco Sciancone

RM/mm
Dear Dr Matteo Bonetti,

My name is Mario Messina and until March 2007 you treated me with a cycle of oxygen ozone therapy (7 injections) at the City of Brescia Clinic, finally with great benefit. I have followed in the press the different acknowledgements you have received and seen on Internet sites how busy you are as a speaker in different congresses in Italy and abroad until late October. As agreed during our last telephone conversation in March last year, I had a follow-up MR scan which I would like you to see, if you agree, as soon as you are back at work at the City of Brescia Clinic. At the moment I am well and not long ago I went back to playing sports and I have no particular physical problems. I look forward to hearing from you and God bless you.

Mario Messina

PS: Please say hello to Dr. Carlo Giuntini from Vicenza – another person miraculously healed.

Dr Bonetti, good morning,

I am writing to tell you that I am definitely better and that your ozone treatment has given me a great boost of recovery. I am continuing treatment with Dr Morosi but I would say that the pain has been decidedly... tamed.

So once again THANK YOU in capital letters! Long live ozone!!!

With kind regards,

Vittorio Peretto
Background: To investigate the effect of oxygen-ozone (O$_2$-O$_3$) injection on thoracolumbar intervertebral disc herniation (IVDH) in dogs.

Materials and Methods: Ten herniated discs of five dogs were treated with percutaneous injection of an O$_2$-O$_3$ gas mixture with O$_3$ concentration of 32 microg/microl intradiscally (1.5-2 microl) under fluoroscopy guidance.

Results: Five weeks after treatment, the mean size of herniated discs was measured by computed tomography and showed significant reduction of disc volumes in all animals (8.8%+/-3.82%). The degree of shrinkage was negatively linearly correlated with disc mineralization (correlation coefficient=-0.636) and statistically significant at p<0.05. All five dogs regained their gait function and none recurred.

Conclusion: We conclude that intradiscal O$_2$-O$_3$ injection can decompress affected discs by disc shrinkage.

How an ill-conceived methodological approach can condemn the medical use of ozone therapy

V. BOCCI, V. TRAVAGLI

Department of Physiology, Department of Pharmaceutical Chemistry and Technology, University of Siena; Siena, Italy


We have clarified the role of the ozone concentration in relation to the resistance of human erythrocytes in whole human blood or in blood diluted either in saline or in distilled water.

Spectrophotometric data related to haemoglobin were evaluated by exposing samples of fresh human blood directly to ozone doses (ratio 1:1 volume), within the therapeutic range (0.21–1.68 mM) and to one toxic dose (3.36 mM). Furthermore, the same determinations have been carried out after previous dilution of the same blood with either pure water or physiological saline (1 ml blood + 29 ml diluent) followed by ozonation with the above reported ozone doses. Addition of
either saline or water implies a dilution of plasma antioxidants and also total haemolysis after water dilution. Particularly the latter case represents a most unphysiological situation because the osmotic shock causes the solubilization of the erythrocytic content. While it is possible to demonstrate that after haemolysis there is an ozone-concentration dependent transformation of some oxyhaemoglobin to methaemoglobin, no such process occurs after ozonation of whole blood.

The results of this study fully confirm our previous data that judicious ozone doses neither damage erythrocytes, nor induce oxidation of intracellular haemoglobin. We hope that our conclusions will definitively clarify the absence of toxicity of ozonotherapy.

A physicochemical investigation on the effects of ozone on blood
VALTER TRAVAGLI, IACOPO ZANARDI, ANTONELLA SILVIETTI, VELIO BOCCI
Department of Pharmaceutical Chemistry and Technology, University of Siena, Siena, Italy

Ozonation of either human whole blood or saline-washed erythrocytes causes considerable damage to the latter and this result has opened a controversy. With the benefit of hindsight, it appears logical that once erythrocytes are deprived of the potent antioxidants of plasma, they become very sensitive to the oxidant effects of ozone.

The aim of the present work was to perform a physical-chemical evaluation of some critical parameters able to clarify this issue.

We have ascertained that when whole blood is exposed to the appropriate ozone doses used in human therapy, no damage ensues while saline-washed erythrocytes undergo conspicuous haemolysis.

The dogma that ozone is always toxic is incorrect because its reactivity below the concentration of 80 µg/mL can be controlled by the plasmatic antioxidant system.

Oxygenation–Ozonation of Blood During Extracorporeal Circulation: In Vitro Efficiency of a New Gas Exchange Device
VELIO BOCCI, IACOPO ZANARDI, VALTER TRAVAGLI, NICOLA DI PAOLO
Department of Physiology, Department of Pharmaceutical Chemistry and Technology, Dialysis and Nephrology Unit, University of Siena; Siena, Italy

We have investigated the performance of a new gas exchange device (GED), named L001, specifically devised for the ozonation of human blood during extracorporeal circulation. This procedure, defined with the acronym “EBOO,” means “extracorporeal blood oxygenation-ozonation.”

The innovative GED is made of microporous, ozone-resistant, polipropylene hollow fibers with an external diameter of 200 µm, a thickness of 50 µm, and a membrane surface area of 0.22 m².

The material is coated with phosphorylcholine on the external side in contact with the circulating blood, while a gas mixture, necessarily composed of medical oxygen and ozone (about 99 and 1%, respectively), flows inside the fibers in opposite direction.

The new GED has been tested by using a buffered saline solution containing KI and by varying
several parameters, and it has shown to be very versatile and efficient. Its main characteristics are minimal foreign surface contact, high gas transfer, and negligible priming volume. This device appears to be a practical, nontoxic, and rather inexpensive tool for performing ozonation of blood for already defined human diseases.

**Estudio prospectivo y aleatorizado en pacientes con lumbalgias o lumbociatálgias tratados con ozonoterapia**

*Prospective and randomized study in patients with low back pain or sciatic pain with ozonetherapy treatment*

J.C. ANSEDE ALONSO, M. CONTRERAS JOYA, S. PÉREZ HIDALGO

Servicio COT, Unidad de Columna, Hospital FREMAP; Sevilla, España

Patología del Aparato Locomotor 5, pp. 46-54, 2007 (Original)

**Is it true that ozone is always toxic? The end of a dogma**

VELIO BOCCI

Department of Physiology, University of Siena; Siena, Italy

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CORSO DI PERFEZIONAMENTO IN OSSIGENO OZONOTERAPIA MEDICA

Anno Accademico 2007/2008

Art. 1 - Oggetto del bando
L’Università degli Studi di Siena istituisce, per l’A.A. 2007/2008, il Corso di Perfezionamento in Ossigeno Ozonoterapia medica.

L’ozonoterapia è una pratica ampiamente diffusa presso gli ambulatori di medicina generale e specialistica.

Particolarmente nell’ultimo decennio, grazie alle indagini biologiche e cliniche svolte presso l’Università di Siena, tale pratica è diventata un’importante strumento per il trattamento di vari tipi di patologie.

Il corso prevede un approccio ampio e vario per evidenziare gli aspetti biochimici e farmacologici dell’ozonoterapia, con un adeguato numero di ore dedicate a svolgere tale pratica, ed a evitare la comparsa di complicanze dovute a imperizia medica.

Il corso prevede pertanto un corso di base di biochimica, con un miglioramento sintomatologico nella maggior parte dei pazienti. E’ tuttavia necessario che il medico acquisisca le competenze necessarie per svolgere tale pratica.

La Direzione del Corso è stabilita presso il Dipartimento di Chirurgia e Bioingegneria dell’Università degli Studi di Siena, Policlinico Le Scotte - Viale Bracci - Siena. Tel.: 0577/438739. Fax: 0577/585235. E-mail: borrelli@unisi.it.

Referente del Corso è la Dott.ssa Emma Borrelli. Tel.: 348/6737259. Fax: 0577/585235. E-mail: borrelli@unisi.it.

Il Corso ha una durata di 12 mesi.

Art. 2 - Requisiti
Per l’iscrizione al Corso è richiesto il possesso di:
1. laurea conseguita secondo gli ordinamenti didattici previgenti al decreto ministeriale 3 novembre 1999, n. 509 in Medicina e Chirurgia e in Odontoiatria e Protesi Dentaria;
3. di diploma di abilitazione alla professione di medico chirurgo e di odontoiatra.

I suddetti requisiti dovranno essere presentati alla data di scadenza del termine utile per la presentazione delle domande di iscrizione al Corso. Differita il prelievo dei requisiti previsti gli ordinamenti, l’iscrizione potrebbe essere respinta, nel qual caso il medico dovrà allegare alla domanda di iscrizione un certificato di invalidità indicante la percentuale riconosciuta dalle competenti autorità.

Il Corso individuerà i criteri oggettivi con cui attribuire i benefici di cui sopra. A tal fine lo studente dovrà allegare alla domanda di ammissione un certificato di invalidità indicante la percentuale riconosciuta dalle competenti autorità.

Il Corso ha una durata di 12 mesi.

Art. 3 - Presentazione delle domande
La domanda di iscrizione, redatta in carta resa legale con marca da bollo dell’importo previsto dalla normativa vigente, indirizzata al Rettore dell’Università degli Studi di Siena, dovrà essere presentata direttamente o spedita per posta a mezzo raccomandata con avviso di ricevimento all’Ufficio Formazione e Post Laurea (Centro Didattico - Policlinico Le Scotte - Strada delle Scotte - 53100 Siena. Tel.: 0577/233109. Fax: 0577/233408. E-mail: post-laurea-medicina@unisi.it entro il termine perentorio del 8 novembre 2007.

Per le domande presentate direttamente o spedita per posta, la ricevuta della data di ricevimento e l’imbarco a data di ricevimento dell’Ufficio Formazione e Post Laurea, per quelle inviate per posta, il timbro a data dell’Ufficio Postale accettante. Nel caso di invio tramite posta l’Amministrazione declina ogni responsabilità per la mancata ricezione delle domande derivante da responsabilità di terzi o da cause tecniche che rendessero impossibile la ricezione. Per essere certi della effettiva ricezione e della correttezza della propria domanda, gli interessati potranno rilasciare direttamente all’Ufficio Formazione e Post Laurea.

La domanda di iscrizione, redatta in carta resa legale con marca da bollo dell’importo previsto dalla normativa vigente, indirizzata al Rettore dell’Università degli Studi di Siena, dovrà essere presentata direttamente o spedita per posta a mezzo raccomandata con avviso di ricevimento all’Ufficio Formazione e Post Laurea (Centro Didattico - Policlinico Le Scotte - Strada delle Scotte - 53100 Siena. Tel.: 0577/233109. Fax: 0577/233408. E-mail: post-laurea-medicina@unisi.it entro il termine perentorio del 8 novembre 2007.

Per l’iscrizione al Corso è richiesto il possesso di:
• dichiarazione sostitutiva di certificazione (ai sensi del D.P.R. del 28 dic. 2000, n° 445 art. 46) dei requisiti di cui all’art. 2 comma 1 (Allegato B);
• curriculum vitae et studiorum
• copia di un documento di identità personale in corso di validità
• copia della ricevuta dell’avvenuto pagamento delle tasse di iscrizione
• copia del Codice Fiscale.

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La Direzione del Corso è stabilita presso il Dipartimento di Chirurgia e Bioingegneria - Sezione di Chirurgia Cardiotoracica dell’Università degli Studi di Siena, Policlinico Le Scotte - Viale Bracci - Siena. Tel.: 0577/585731. Fax: 0577/585235. E-mail: borrelli@unisi.it.

Tutor del Corso sono la Dott.ssa Emma Borrelli e il Dott. Josip Buric. Tel.: 0577/585731. E-mail: borrelli@unisi.it.

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Art. 3
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Art. 4 - Tasse di iscrizione
La tassa di iscrizione ammonta a euro 980,00 al netto di qualsiasi onere ed eventuali commissioni bancarie. Tale somma dovrà essere versata in un’unica rata all’atto del perfezionamento della pratica di iscrizione. Rientrando i Corso nell’attività istituzionale dell’Ateneo, e non in quella commerciale, le tasse di iscrizione restano al di fuori del campo di applicazione I.V.A., pertanto non potrà essere rilasciata alcuna fattura. In caso di rinuncia l’amministrazione si riserva la possibilità di autorizzare il rimborso per gravi e giustificati motivi nel caso in cui i corsi non abbiano avuto inizio.

Art. 5 - Organi del Corso
Sono organi del Corso:
- il Direttore eletto dal Consiglio del Corso tra i docenti dell’Università degli Studi di Siena
- il Direttore del Corso, composto da tutti i docenti interessati al corso stesso.

Art. 6 - Percorso formativo
La frequenza è obbligatoria. Sono permessi assenze giustificabili fino ad un massimo del 20% delle attività previste. Il Corso avrà inizio il 24 novembre 2007 e termine nel mese di novembre 2008. Il calendario sarà comunicato dalla Direzione del Corso. Sede prevalente di svolgimento delle attività didattiche è Dipartimento di Chirurgia e Bioingegneria - Sezione di Chirurgia Cardotoracica - Siena. Vengono individuate all’interno del percorso formativo i seguenti insegnamenti:
Insegnamento basi biochimiche dell’ozono: docente Prof. Velo Bocci
Insegnamento grande e piccola autoemoterapia: docente Dr.ssa Emma Borrelli
Insegnamento ozonoterapia nelle patologie ortopediche: docente Dr Roberto Cardelli
Insegnamento ozonoterapia nelle patologie neurochirurgiche: docente Dr Josip Buric
Insegnamento ozonoterapia nelle ulcere ed in angiologie: docente Dr.ssa Maria Letizia Iabichella
Insegnamento ozonoterapia in medicina estetica: docente Dr Mario Sritto

Art. 7 - Verifica finale
La verifica finale consiste nella presentazione di una tesi. Il risultato della verifica finale dovrà essere sintetizzato in uno dei seguenti giudizi: sufficiente/buono/distinto/ottimo salvo diverse disposizioni previste dall’organo competente.

Art. 8 - Rilascio del titolo
A conclusione del Corso, agli iscritti che a giudizio del Consiglio hanno svolto le attività ed adempiuto agli obblighi previsti, è rilasciato dal Direttore del Corso un attestato di frequenza secondo le leggi vigenti in materia. Il rilascio dell’attestato è subordinato ad apposita richiesta da effettuarsi su modulo disponibile presso l’Ufficio Formazione e Post Laurea.

Art. 9 - Trattamento dei dati personali
Ai sensi del D.Lgs 30.06.2003 n. 196, i dati personali forniti dai candidati saranno raccolti presso l’Università degli Studi di Siena – Area servizi agli studenti - per le finalità di gestione dell’ammissione e saranno trattati anche successivamente alla eventuale iscrizione al Corso, per finalità inerenti e conseguenti alla gestione del rapporto medesimo. L’interessato gode dei diritti previsti dall’art. 7 del citato D.Lgs tra i quali figura il diritto di accesso ai dati che lo riguardano. Tali diritti potranno essere fatti valere nei confronti dell’Università degli Studi di Siena - Via Banchi di Sotto n.55 - Siena, titolare del trattamento.
Reportage

The honourable Bellotti outlines legislation on ozone.

Figures 1, 2 and 3 - Workshop

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E-mail: info@xrayservice.it
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Dr Iliakis, Dr Cardelli

Dr Bocci

Dr Maggiorotti, Dr Leonardi

Dr Bonetti, Dr Barco

Dr Gjionovic, Dr Scarchilli
Reportaje
Dr De Lucas, Dr Bonetti, Dr Galbán, Dr Muto

Dr Galbán, Dr Bonetti,

Dr De Lucas, Dr Bonetti, Dr Galbán
ITINERANT COURSE OF
OXIGEN-OZONE THERAPY
SEPTEMBER 29, 2007
Napoli

Reportage

Dr Bonaldi, Dr Pellicanò

Dr Guarnieri

Prof. Gallucci, Dr Pellicanò

Prof. Sossio Cirillo, Dr Muto
Palmyra

Palmyra is one of those mythical places that alone merit a visit to Syria. From Damascus a road leads directly across the steppe to this oasis, a place where the clear blue sky blends magically with the warm colour of its stone and the green of its palm-trees. Located halfway between the Mediterranean sea and the Euphrates river, Palmyra boasts underground hot-water springs making it an ideal halt for ancient caravans moving between the sea and the river. Palmyra’s magnificent well-conserved ruins, namely the Bel Temple, the Arc of Triumph, the Congress Council and the Market Place, give a good idea of the city’s greatness when it was ruled by Queen Zenobia in the 2nd century BC.

Dr Bonetti, Dr Andreula and all the medical staff at the Damascus military hospital.

Dr Bonetti and Dr Andreula with paramedical staff at the Damascus military hospital after the oxygen-ozone treatments.
Dr Bonetti, Syrian Ministry of the Interior Bassam Almajeed and Dr Andreula

Palmyra – The Roman City

Syria

Palmyra, The Roman City

Syria

Woman making bread
3rd International Endovascular Surgery & Therapeutic Radiology Course
Spine and Spinal Cord
April 27, 2008
Saint Petersburg, Russia

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## I Congreso Nacional de la FEOT
### II WFOOT Meeting
Madrid, 4-5-6 diciembre 2008

### Pre-Programa

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<td>Presentación de la FEOT</td>
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<td><strong>21:00:00</strong></td>
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<td>Cena de Gala</td>
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**Más información:**
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World Federation of Oxygen - Ozone Therapy

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