

FIRST INTERNATIONAL CONGRESS OF AEPROMO

"NEW HORIZONS FOR THE OZONE THERAPY"

Congress Palace, Pontevedra (Galicia, Spain)
Thursday 4th, Friday 5th and Saturday 6th June, 2009

Ozone Therapy in the Management of Sport Pain
Role of Mitochondria



Lamberto Re¹, Gregorio Martínez-Sánchez² and Giuseppe

7/19/09

Malcangi³

Summary:

Main biological effects elicited during exposure to O2/O3

Substrates

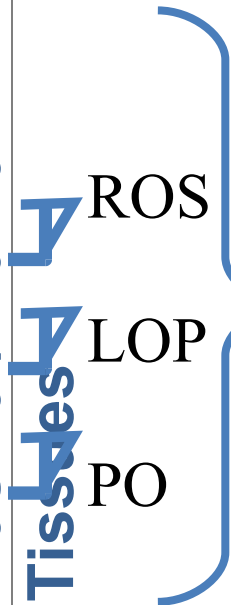
Messengers

Targets

Functional modifications



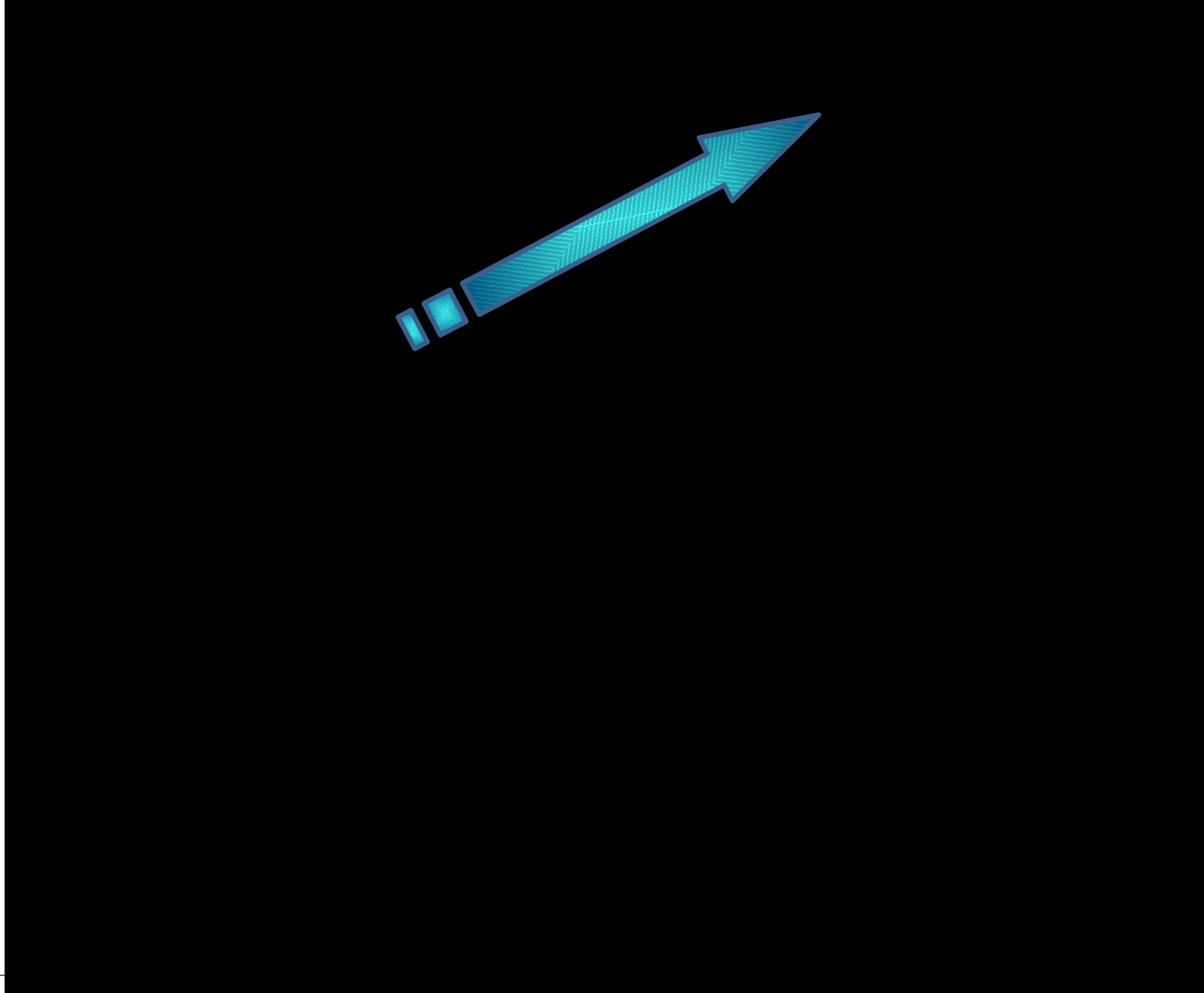
Plasma / Human Tissues



Erythrocytes	Improve O2 delivery
Leukocytes	Immune modulation
Platelets	Release of autacoids and growth factors
Endothelium	Modulation of eNOS
Bone Marrow	Generation of super-gifted erythrocytes
Other	Release of stem cells
	Upregulation of antioxidant enzymes

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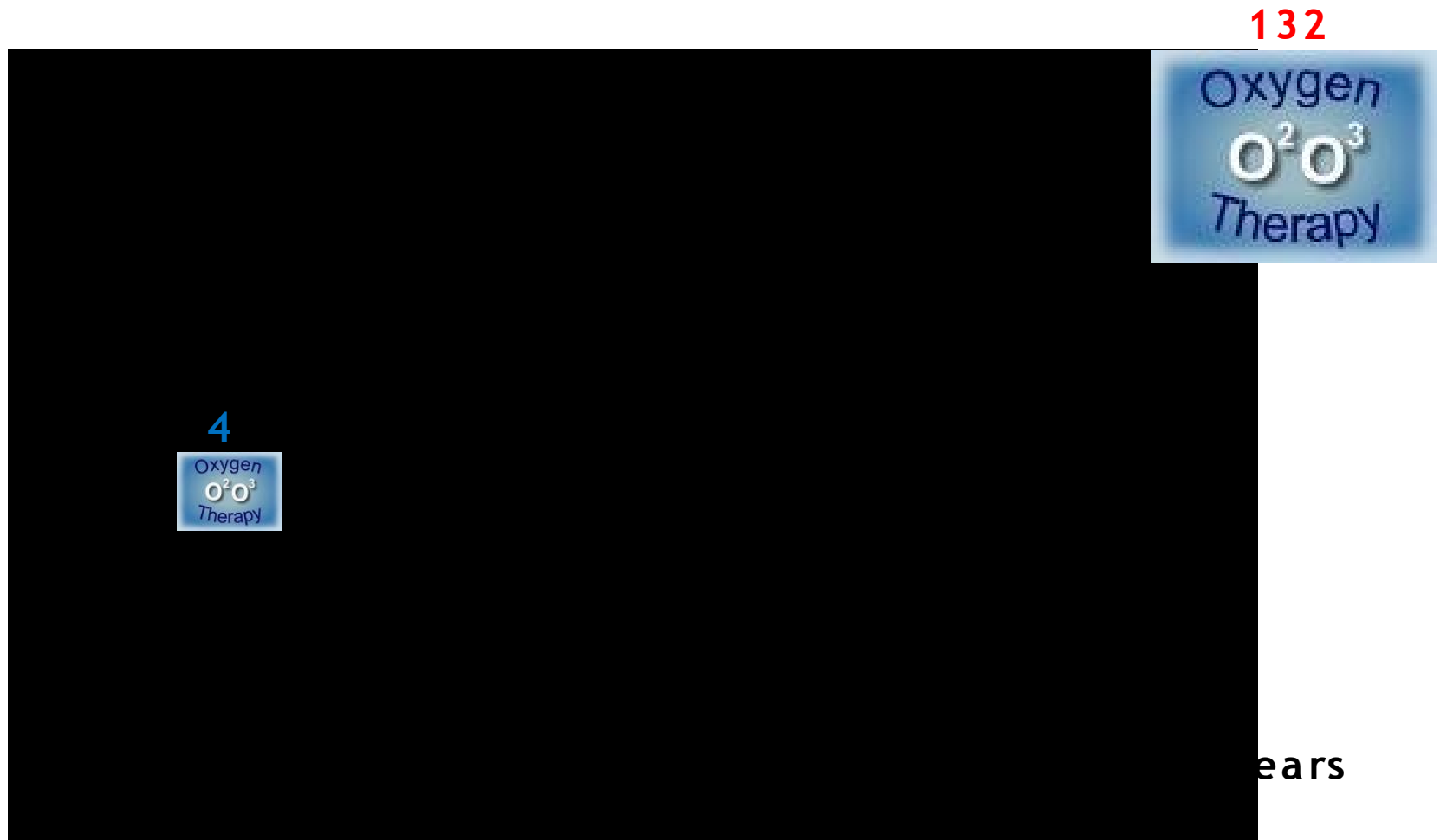
Number of articles per year, relative to



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Data from MedLine PubMed, May

Number of articles per year, related to “ozone in medicine”

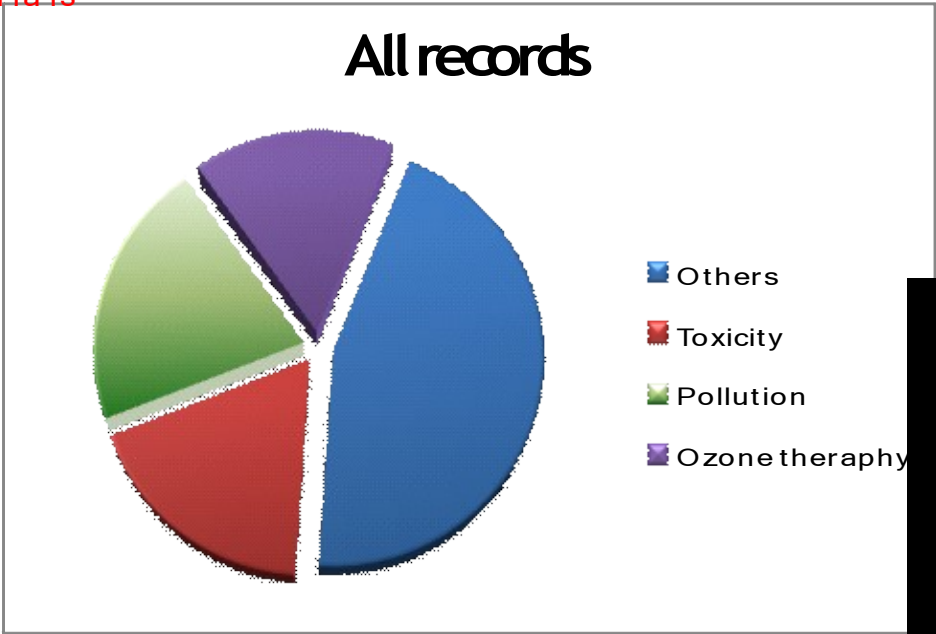


7/19/09

Data from Web Sciences, May

Evolution in Number of articles related to “Ozone / Clinical

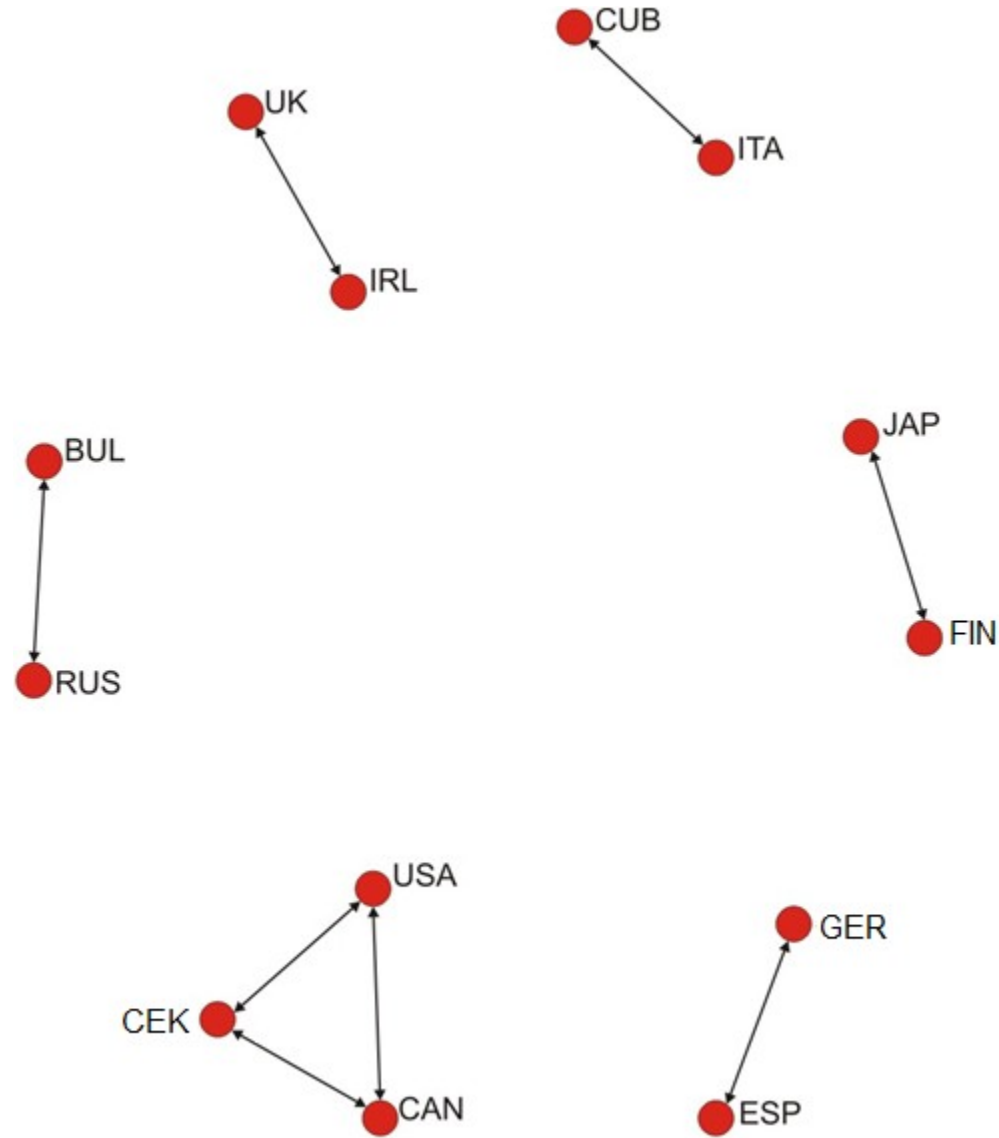
Includes
140 papers
on **Clinical
Trials**



7/19/09

Data from MedLine PubMed, March

Trends in Ozone International Cooperation Network



Scientific Production in Ozone Therapy by Countries

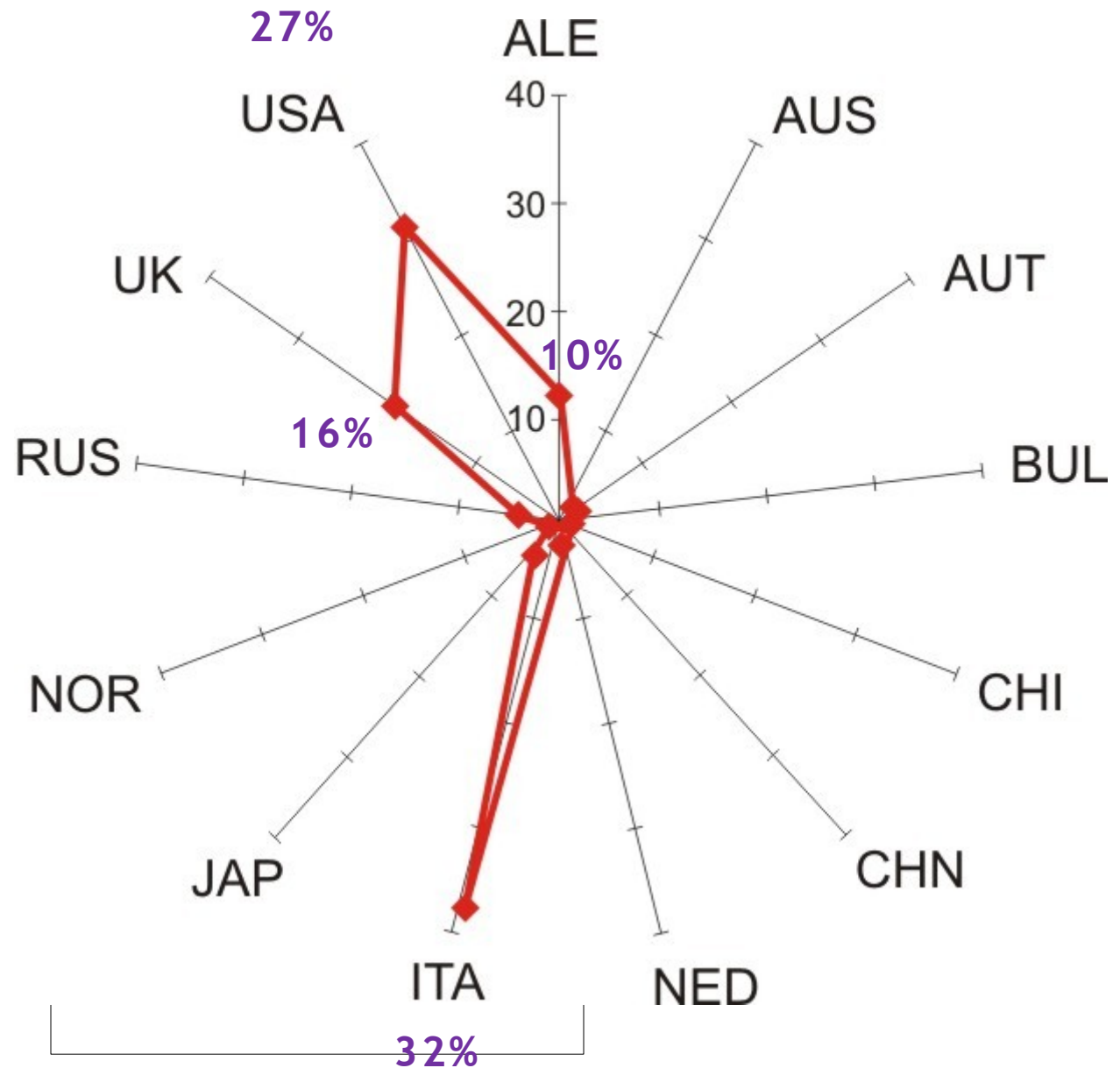
Web of Science 2009



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Scientific
Paper
about
ozone
are
mainly
published
in:

7/19/09



In this presentation we show data collected on patients treated with Ozone Therapy during the last four years for disorders related to pain in sport traumatism (Sport T, 384 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.

Study Design

The study was 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.

All patients signed an informed consent 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.

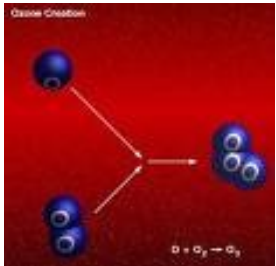
Inclusion criteria: Adult patients of both gender and different ethnic with diagnosis of sport trauma associated with physical pain, that attended to Medinat Clinic (Ancona, Italy) during October 2004 to October 2008.

Exclusion criteria: Patients must not meet any of the following criteria: severe septic conditions, hypersensitivity to the medication that will be used, hepatic dysfunction, renal failure (serum creatinine level > 1.32 μ mol/L), pregnancy, hypertiroidism, 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 immunosuppressive agent or anticonvulsant, concurrent participation in another clinical study or current treatment with an investigational drug.

Patients were treated twice a week with O₂/O₃ mixture in 12-15 consecutive sessions (with an ozone dose of 25-50 mL, ozone concentration: 8-12 □ g/L, 3-5 mL per application).



Ozone obtained from medical grade oxygen represented about 0.4-0.5 % of the gas mixture. The ozone concentration was measured by using a build-in UV spectrophotometer at 254 nm.



Percutaneous injection was done using 30 mL disposable syringes (Ozone Resistant) and 30Gx1/2 disposable needle inserted in the surrounding of the affected area (Local Puncture).

Achille's Tendon

Injuries



30G 13mm – 27G 6mm

10 □g/ml

20 cc

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Results

Baseline patient characteristics

In subject was not detected hypertension, renal dysfunction, diabetes or cardiovascular diseases.

A mean of 10-12 session of O2/O3 treatment was used to reach therapeutic success.

Local puncture was the main important clinical protocol

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Characteristics		Sport Traum. (n=384)
Age (years)	Median	30*
	Minimum	16
	Maximum	46*
Gender (%)	Female	20*
	Male	80*
Concomitant treat.(%)	Analg./ Antinf.	23
	Vit. / Supplem.	6
	Phys. Ther.	26
Prev. History n(%)	Surgerya	1(0)*
	Hypertensionb	0*
	Renal dysfunction c	0*
	Diabetesd	0*
	Cardiov. diseasee	0*
Therap. protocol	Number of session, median (min, max)	10(5-16)
	Local procedure (LP/B%)	100/65
	Systemic procedure (H/M/R%)	15/30/0*

Time course of the clinical evolution (according OPRS scale) of pain



In articular pain (knee and shoulders) a satisfactory evolution was also observed. A sustained and significant ($p < 0.05$) improvement was note in both case up-to 6 months of evolution.

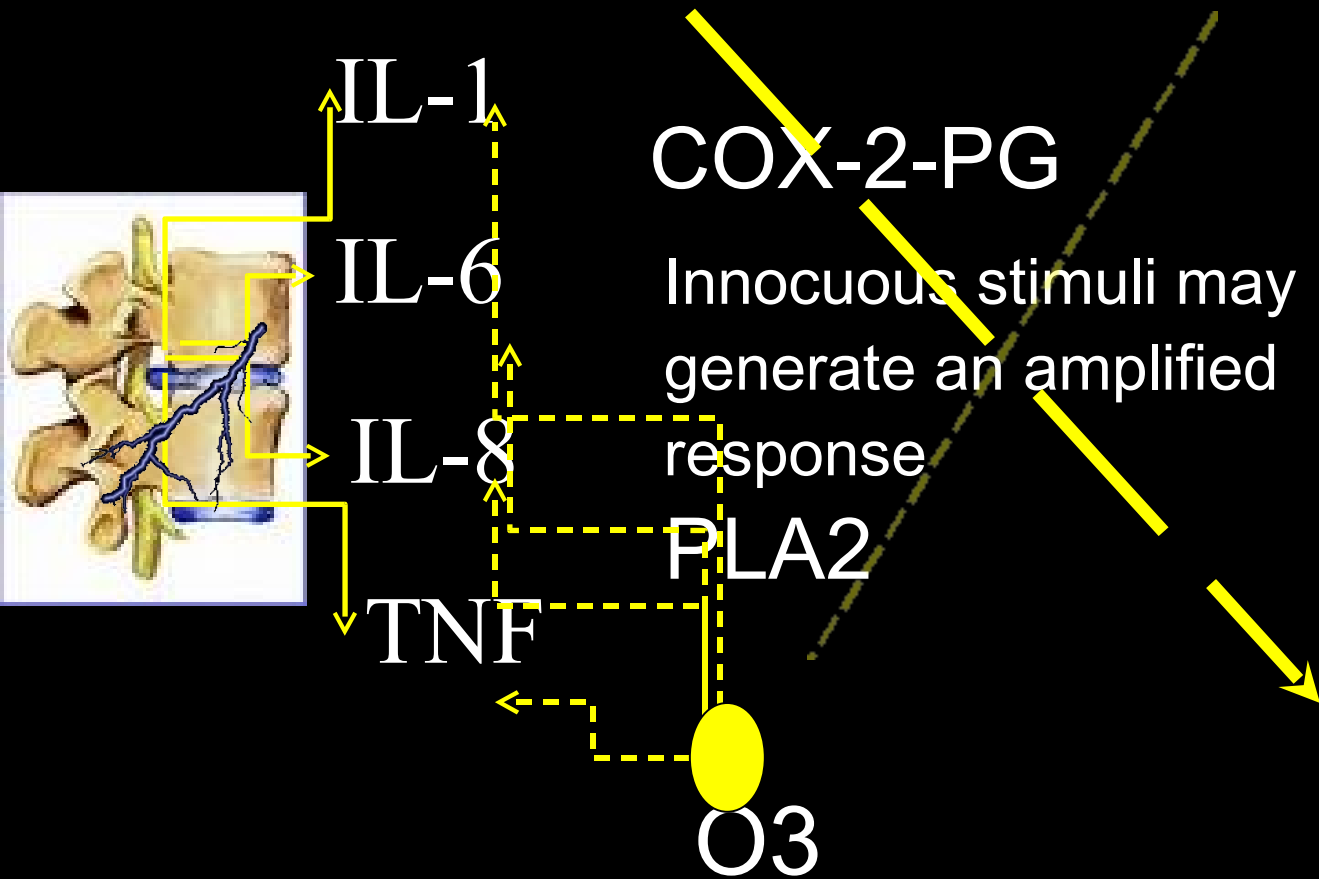
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Time course of the clinical evolution (according OPRS scale) of pain



In non articular pain disorders a significant ($p < 0.05$) positive O2/O3 therapy response was also noted. Tendinitis and miscellaneous non articular pain/inflammation get at 1-2 years of evolution the OPRS category “good” An exceptional and sustaining favourable evolution was observed in pubalgia, just 2 weeks after the treatment a

O3 inhibit pain peripheral



Peripheral sensitization
PAIN



J Bone Joint Surg Am (2006)

Arterioscler Throm Vasc Biol 2006

Ozone usually mostly react in the painful area



Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar



Neuropharmacology and Analgesia

A single subcutaneous injection of ozone prevents allodynia and decreases the over-expression of pro-inflammatory caspases in the orbito-frontal cortex of neuropathic mice

Carlo Fuccio^a, Carlo Luongo^b, Paola Capodanno^b, Catia Giordano^a, Maria Antonietta Scafuro^{a,b},
Dario Siniscalco^a, Biagio Lettieri^b, Francesco Rossi^a, Sabatino Maione^{a,*}, Liberato Berrino^a

^a Department of Experimental Medicine, Section of Pharmacology "L. Donatelli", Faculty of Medicine and Surgery, Second University of Naples, Via Costantinopoli, 16 80138 Naples, Italy

^b Department of Anaesthesia and Intensive Care, Second University of Naples, Via De Crecchio, 80138 Naples, Italy

ARTICLE INFO

Article history:

Received 20 October 2008

Accepted 26 November 2008

Available online 6 December 2008

Keywords:

Caspases

Orbito-frontal cortex

Allodynia

Ozone therapy

(Mouse)

ABSTRACT

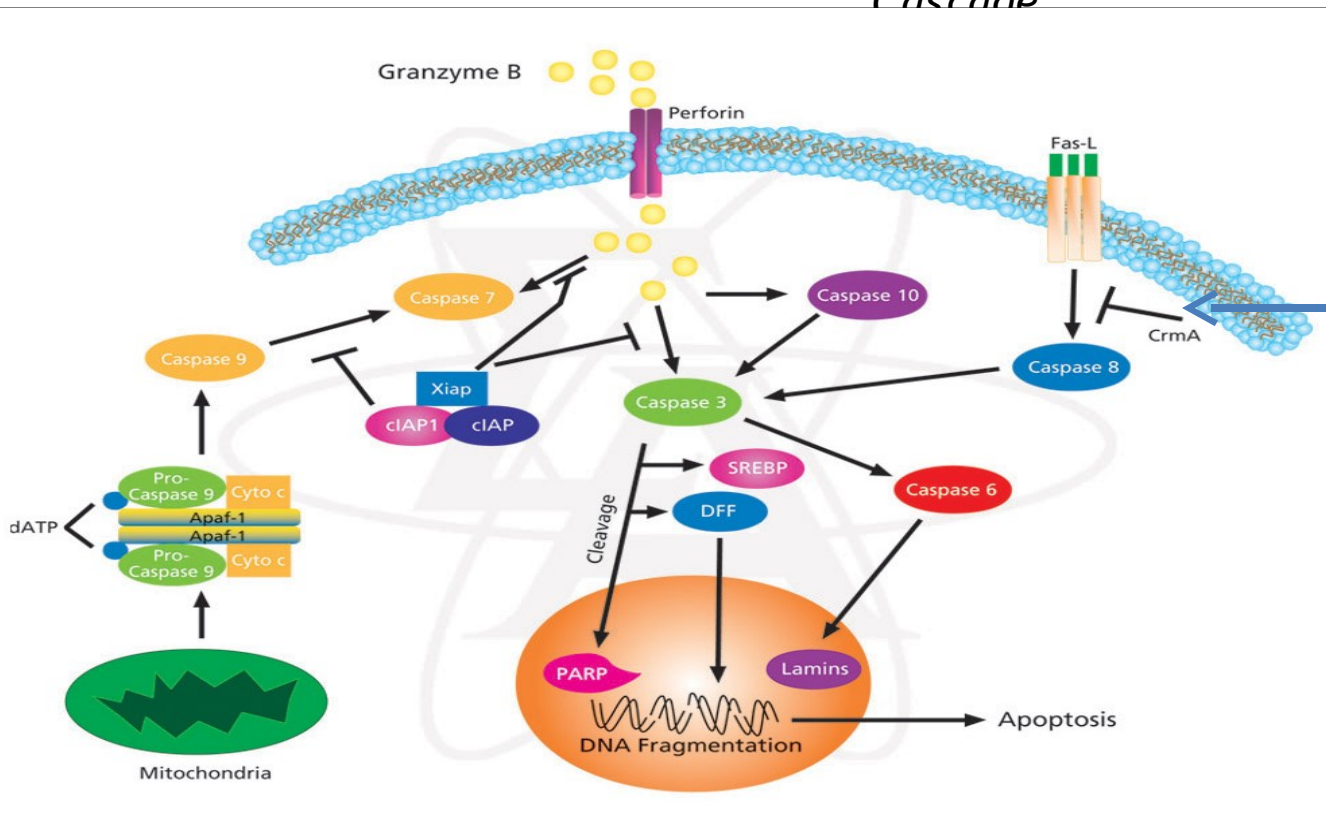
The neuropathic pain model consisting of the spared nerve injury of the sciatic nerve was used in the mouse to examine whether peripheral neuropathy is capable of generating over-expression of pro-inflammatory and pro-apoptotic genes in the orbito-frontal cortex, together with allodynia and hyperalgesia. RT-PCR analysis showed increased expression of *caspase-1*, *caspase-12* and *caspase-8* genes in the orbito-frontal cortex 14 days after spared nerve injury of the sciatic nerve. Conversely, the expression of *caspase-3* was decreased by spared nerve injury of the sciatic nerve in the same brain area. A single subcutaneous injection of ozone performed 12 h after the surgical procedure decreased mechanical allodynia and normalized the mRNA *caspase-1*, *caspase-12* and *caspase-8* gene levels, but did not decrease *caspase-3* level, 14 days post-spared nerve injury. Ozone also reduced IL-1 β staining in the orbito-frontal cortex in neuropathic mice. This study provides evidence that a single subcutaneous administration of ozone decreased neuropathic pain type behaviour, normalized the expression of pro-inflammatory caspases and reduced IL-1 β staining in the orbito-frontal cortex astrocytes in SNI mice. These preliminary data show that peripheral neuropathy induced over-expression of pro-inflammatory/pro-apoptotic caspases in the orbito-frontal cortex and that ozone, by mechanisms that are as yet unknown, can regulate the expression of the genes that play a pivotal role in the onset and maintenance of allodynia.

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We show here that ozone, injected subcutaneously (Muto et al., 2004; Re et al., 2008), prevented the increased mRNA levels of caspase-1, caspase-8 and caspase-12 in the orbito-frontal cortex of SNI mice and prevented the development of allodynia in the same mice.

Collectively, these preliminary data indicate that ozone can be an effective practice for preventing the development of neuropathic pain through complex as yet unexplored mechanisms and, among these, through the modulation of specific pro-inflammatory or pro-apoptotic caspases in the brain.

Caspase Cascade



Ozone block the synthesis of caspases 1, 8, 12



Ozone can be active at mitochondrial level ???

1. Ozone can induce **MnSOD**. Transplant International, 18, 604-612, 2005
2. Ozone modulate **NO**. Liver Int. 2004 Feb;24(1):55-62.
3. Ozone may act as a Potassium channel openers KCOs. Pharm. Res. 45(5), 2002.
4. Ozone vs. **Rotenone damage**. Archives Med Res, 39: 17-26, 2008
5. 4 case report (paper on preparation), Univ. Ancona, 2008

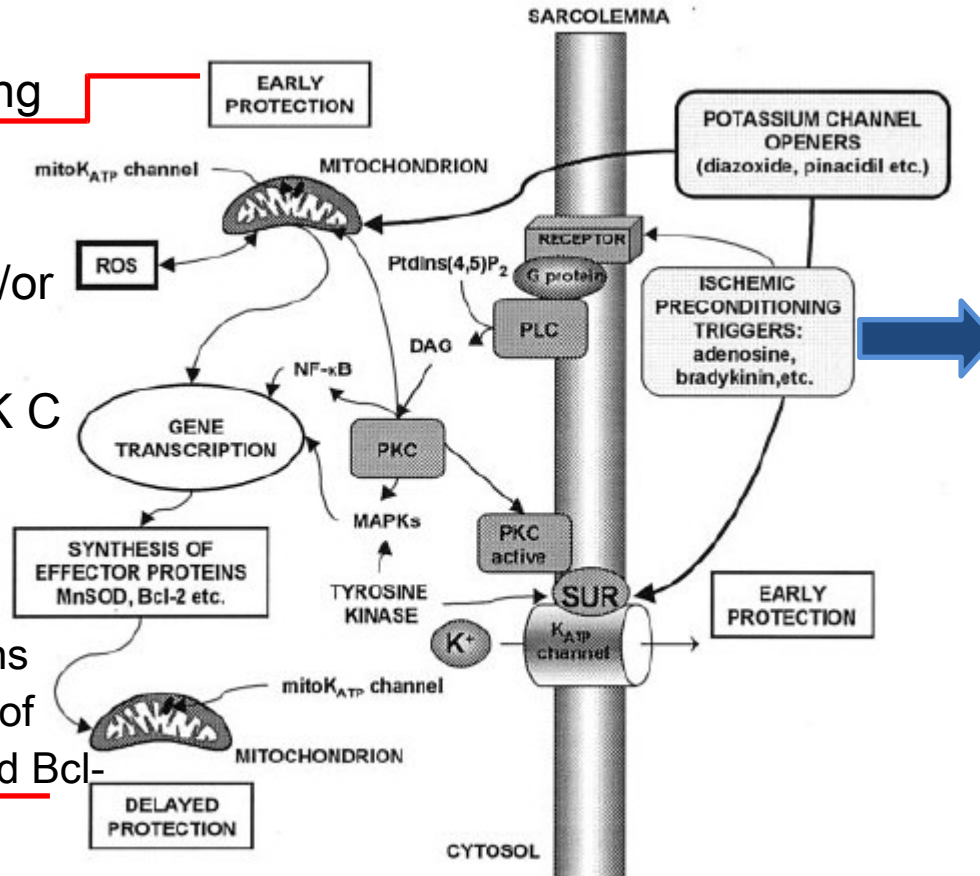
Mitochondrial swelling
could improve
mitochondrial
ATP production and/or
handling.

Ca²⁺ Prot.K C

Expression of proteins
involved in the control of
apoptosis eg. Bcl-2 and Bcl-

XI

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Ozone
Preconditioning act
by similar
mechanisms

Pharm. Res. 2002.

L'associazione MITOCON vi invita il **14 marzo 2008** ad una Giornata di studio sulle Malattie Mitocondriali.

Luogo: Ospedale Bambino Gesù - Piazza S. Onofrio, 4 - 00165 Roma
Foyer Aula Salviani - Padiglione Salviani

I parte - SEMINARIO

L'UTILIZZO DELL'OZONO NEL TRATTAMENTO DEI PAZIENTI MICOONDRIALI

- 10.30 Accoglienza
- 10:45 Presentazione Associazione MITOCON: Obiettivi e programmi per il 2008
Piero Santantonio - Mitocon
- 11:00 Introduzione all'Ozonoterapia: principi e campi di applicazione tradizionali
Lamberto Re - Università di Ancona
- 11:30 Le nuove frontiere dell'applicazione dell' ozonoterapia: le ultime acquisizioni sperimentali e cliniche
G. Sanchez - Università de l'Avana (Cuba)
- 12:00 L'applicazione dell'ozonoterapia alle malattie mitocondriali - Idee per un razionale della terapia e definizione di un percorso sperimentale
E. Bertini - Ospedale Bambin Gesù - Roma
- 12:30 Possibile protocollo sperimentale per l'avvio della sperimentazione clinica
Lamberto Re - Università di Ancona
- 12:45 Dibattito
- 13:30 Chiusura lavori

Colazione di lavoro

Announcement

Mitocon

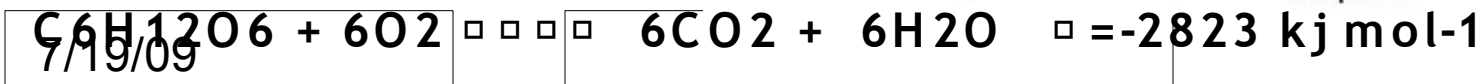
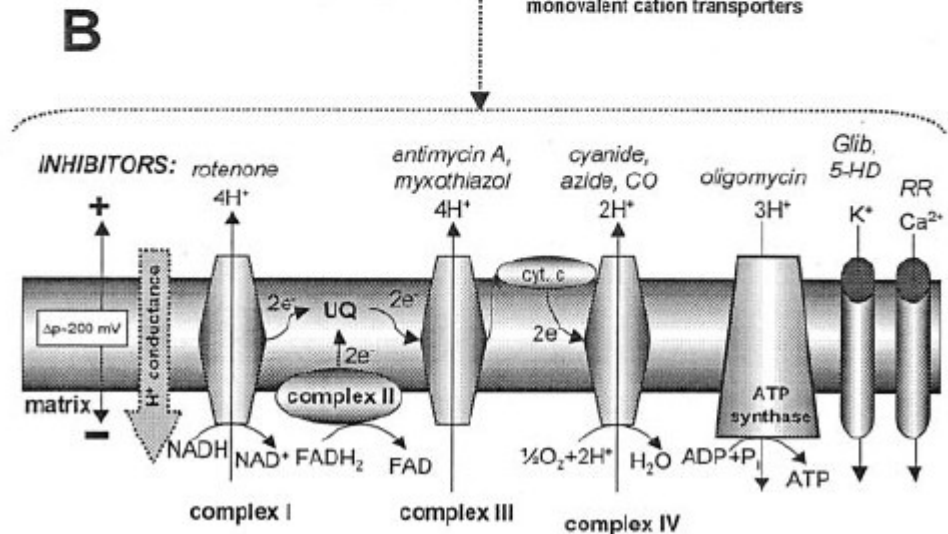
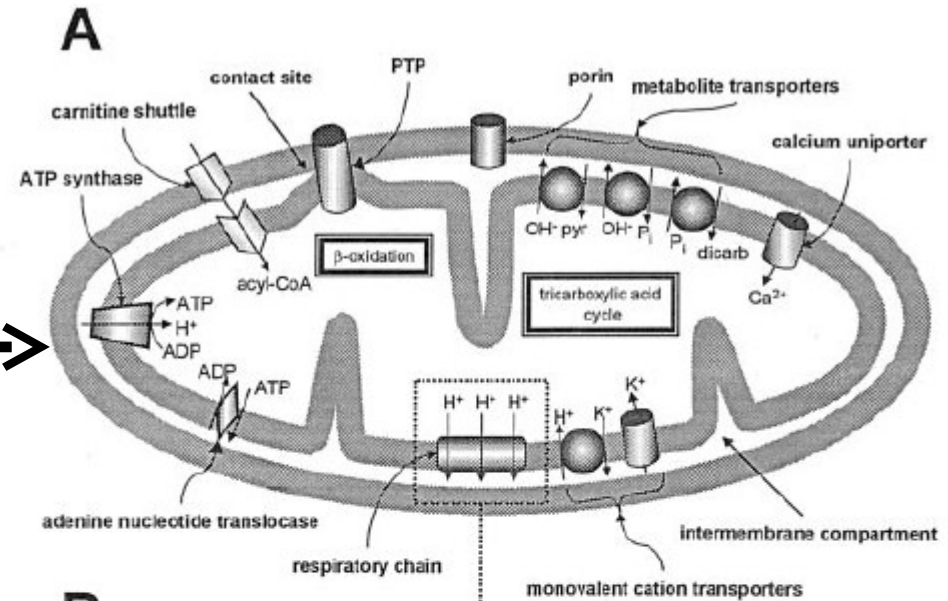
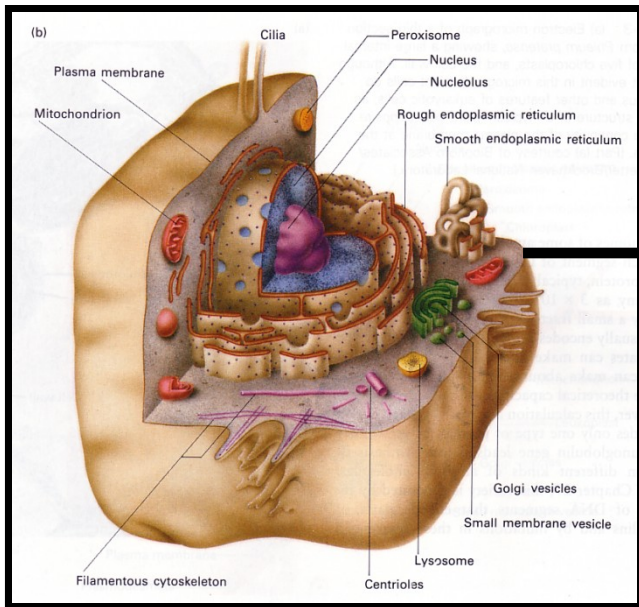
Meeting organized by:

Neurology, Bambin Gesù, Rome

Pediatric Disease, Gaslini, Genova

**Pediatric Neurology, Besta Institut,
Milan**

Schematic representation of the mitochondrion and the respiratory chain



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Mitochondrial diseases are an important cause of morbidity and mortality in both adults and children, with up to **1 / 3500** of the UK population affected. These **neurogenetic disorders** are clinically heterogeneous and associated with an array of genetic defects occurring in both the mitochondrial and nuclear genomes.

Damage Protein Electron transport chain fail Over production of ROS

Diseases
↓



Brain and Muscle Damage

Myoclonic epilepsy and ragged-red fiber disease (MERRF)
Leber's hereditary optic neuropathy (LHNO)
Leigh syndrome

The Effect of Ozone Therapy for Lumbar Herniated Disc

This study is currently recruiting participants

Verified by Kovacs Foundation, May 2009

First Received: November 29, 2007 Last Updated: May 27, 2009

Sponsors and Collaborators:	Kovacs Foundation Fondo de Investigacion Sanitaria Hospital Negrin Hospital Son Llatzer Servicio de Salud de las Islas Baleares (Ib-Salut)
Information provided by:	Kovacs Foundation
ClinicalTrials.gov Identifier:	NCT00566007

Intra-articular Ozone Therapy for Pain Control in Osteoarthritis of the Knee

This study is not yet open for participant recruitment
Verified by Ben-Gurion University of the Negev, January 2009

First Received: January 29, 2009 No Changes Posted

Sponsored by:	Ben-Gurion University of the Negev
Information provided by:	Ben-Gurion University of the Negev
ClinicalTrials.gov Identifier:	NCT00832312

7/19/09

Healozone Study to Evaluate the Safety and Efficacy of the Use of Ozone for Management of Dental Caries

This study is ongoing, but not recruiting participants

First Received: July 1, 2007 Last Updated: February 16, 2009

Sponsors and Collaborators:	Indiana University School of Dentistry Tufts University SUNY School of Dental Medicine
Information provided by:	Indiana University School of Dentistry
ClinicalTrials.gov Identifier:	NCT00495495

Protocol Registration Receipt

06/02/2009

Oxygen - Ozone Therapy in Pain Control of Geriatric Patients

This study is not yet open for participant recruitment.

Verified by Medinat SRL, June 2009

Sponsored by:	Medinat SRL Istituto Superiore di Sanita Università Politecnica delle Marche
Information provided by:	Medinat SRL
ClinicalTrials.gov Identifier:	

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CONCLUSION REMARK

No adverse effects were observed during the ozone therapy in all the patients treated during the last 4 years in the Medinat Clinic (1,800 Patients X 20,000 Ozone Treatments).

In our experience, O2/O3 treatment of pain and inflammatory diseases has revolutionized the approach to radiculopathy and articular disease pain management particularly in the elderly.

O2/O3 is a safer, cheaper and easier to repeat in respect to the treatments currently in use. In addition, O2/O3 therapy does not preclude later recourse to surgery if the patients fail to reach a suitable benefit.

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CONCLUSION

The **recent attention addressed to ozone** by some Excellence Center in the Health Care from different Countries represents **a big chance for all the Ozone Therapists.**

The **multidisciplinary cooperation** in the aim to develop protocols for the treatment of many orphan pathologies must be encouraged to reach finally the most **wide scientific consideration** in fact of Ozone Therapy.

We look forward to reach in the recent future the best results to give us back all the best in relation to the efforts spent since many years in the Scientific and Clinic development of Ozone Therapy.



COMUNE DI CAMERANO

PROVINCIA DI ANCONA

III SETTORE (GESTIONE DEL TERRITORIO E DEL PATRIMONIO)

AUTORIZZAZIONE N. 258

Camerano li 19 marzo 2009

IL RESPONSABILE DI SETTORE

Richiamato il proprio provvedimento n.248 del 13.6.2008 con il quale si autorizzava la sig.ra Elia Cavalieri in qualità di legale rappresentante della ditta Medinat srl all'esercizio, nel proprio ambulatorio di via Fazioli n. 22 di Camerano, all'esercizio di prestazioni mediche specialistiche con l'esclusione delle pratiche di ossigeno ozono terapia;

Vista la nota datata 15.1.2009 protocollata in arrivo da questo Comune in data 20.1.2009 al n.429, con la quale il dottor Lamberto Re, responsabile dello studio medico sito in via Fazioli n.22 di Camerano chiede una nuova autorizzazione nella quale sia prevista la possibilità di praticare nell'ambulatorio privato della ditta Medinat la pratica di ossigeno-ozono terapia;

Visto che in data 12.3.2009 la Regione Marche a seguito di richiesta da parte del Comune di Camerano di parere in merito ha comunicato a questo Comune con lettera di protocollo n.145267 del 12.3.2009 che la pratica di ossigeno-ozono-terapia può essere effettuata in strutture private in quanto non vietata da norme o regolamenti o ordinanze d'urgenza dell'autorità sanitaria;

Ritenuto in attuazione alla pronuncia della regione Marche di rilasciare una nuova autorizzazione di in sostituzione di quella precedente;

Visto l'art.107 del dlgs del 18.8.2000 n.267 che trasferisce ai dirigenti delle amministrazioni i poteri gestionali precedentemente attribuiti al Sindaco da leggi o Regolamenti;

Visto il provvedimento sindacale n.34 del 30.12.2008 con il quale vengono attribuite le funzioni di responsabilità dirigenziale delle Ente per il III settore "Gestione del Territorio e del Patrimonio";

A U T O R I Z Z A

La sig.ra Elia Cavalieri in qualità di legale rappresentante della ditta Medinat srl, nata a Fabriano il 3.12.1954 e residente a Camerano in via Cameranesse 53, all'esercizio di prestazioni mediche specialistiche **comprese** le pratiche di ossigeno-ozono-terapia.

La responsabilità dell'ambulatorio, sito in via Fazioli di Camerano, è affidata al dottor Lamberto Re iscritto presso l'ordine dei medici chirurghi della Provincia di Ancona.

La presente sostituisce ed annulla la precedente autorizzazione n.248 del 13.6.2008.



IL RESPONSABILE DEL III SETTORE

(Geom.Rinaldo Frontalini)

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