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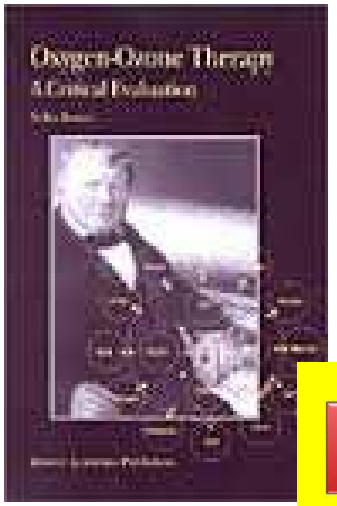

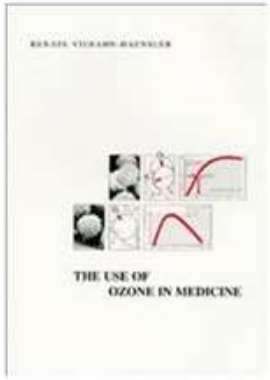

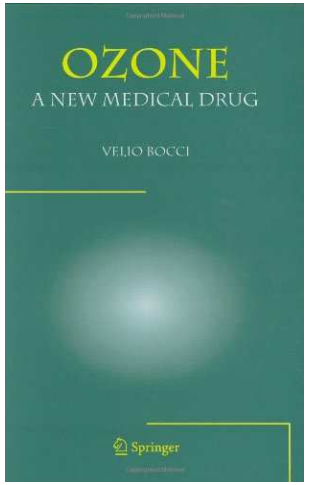

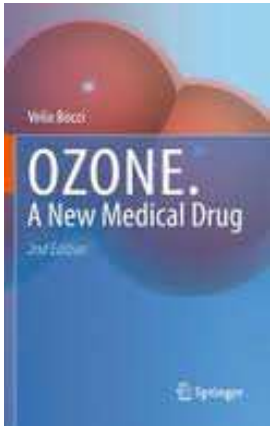

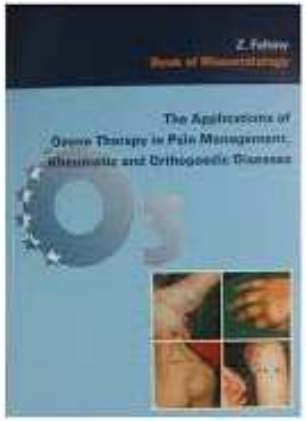

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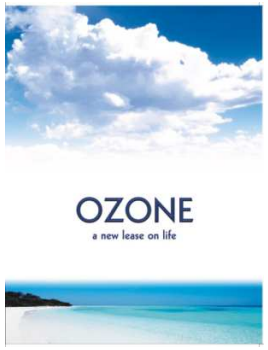

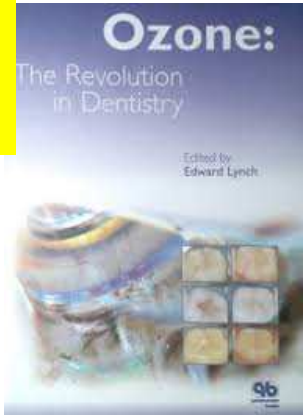

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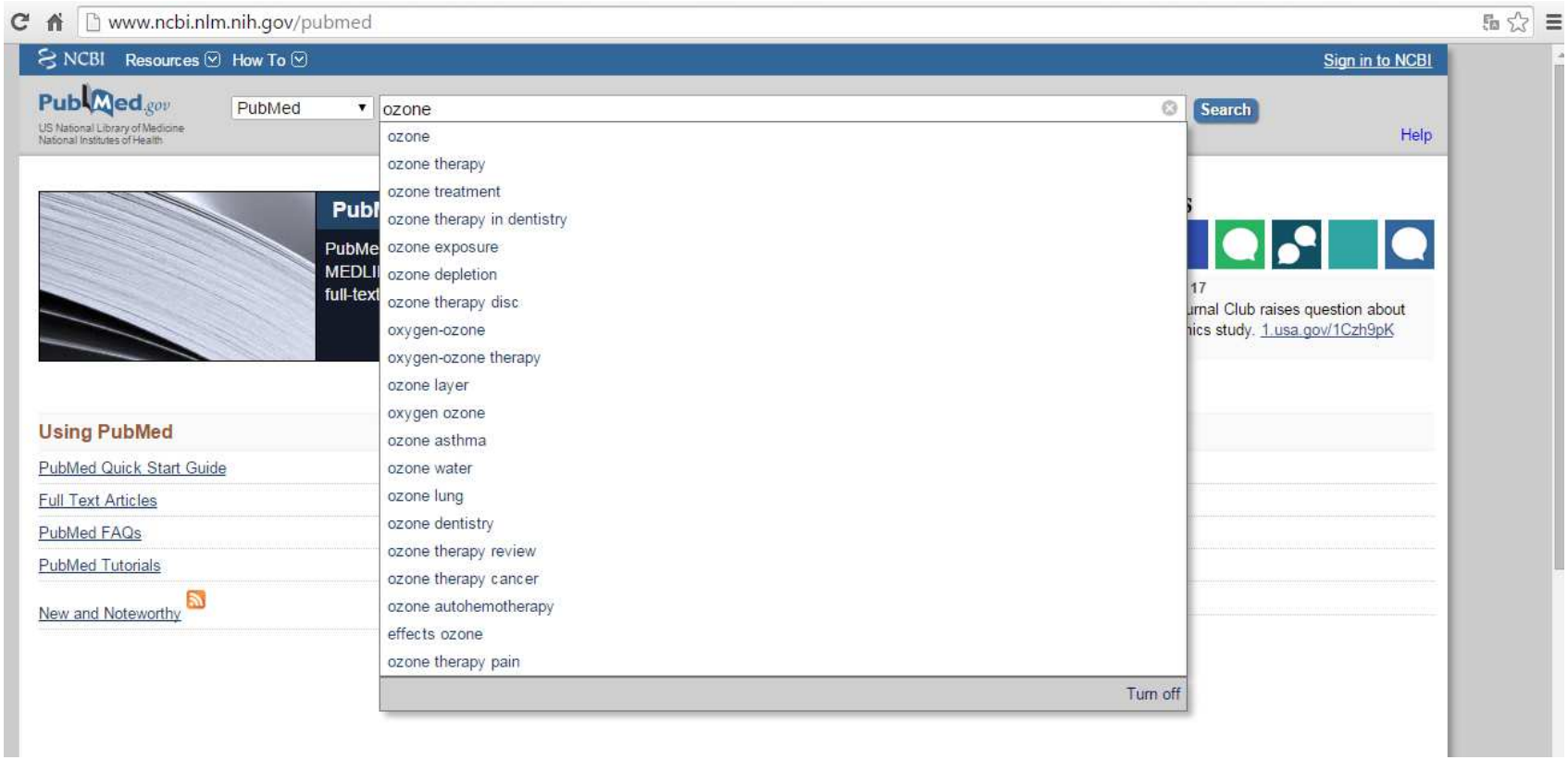

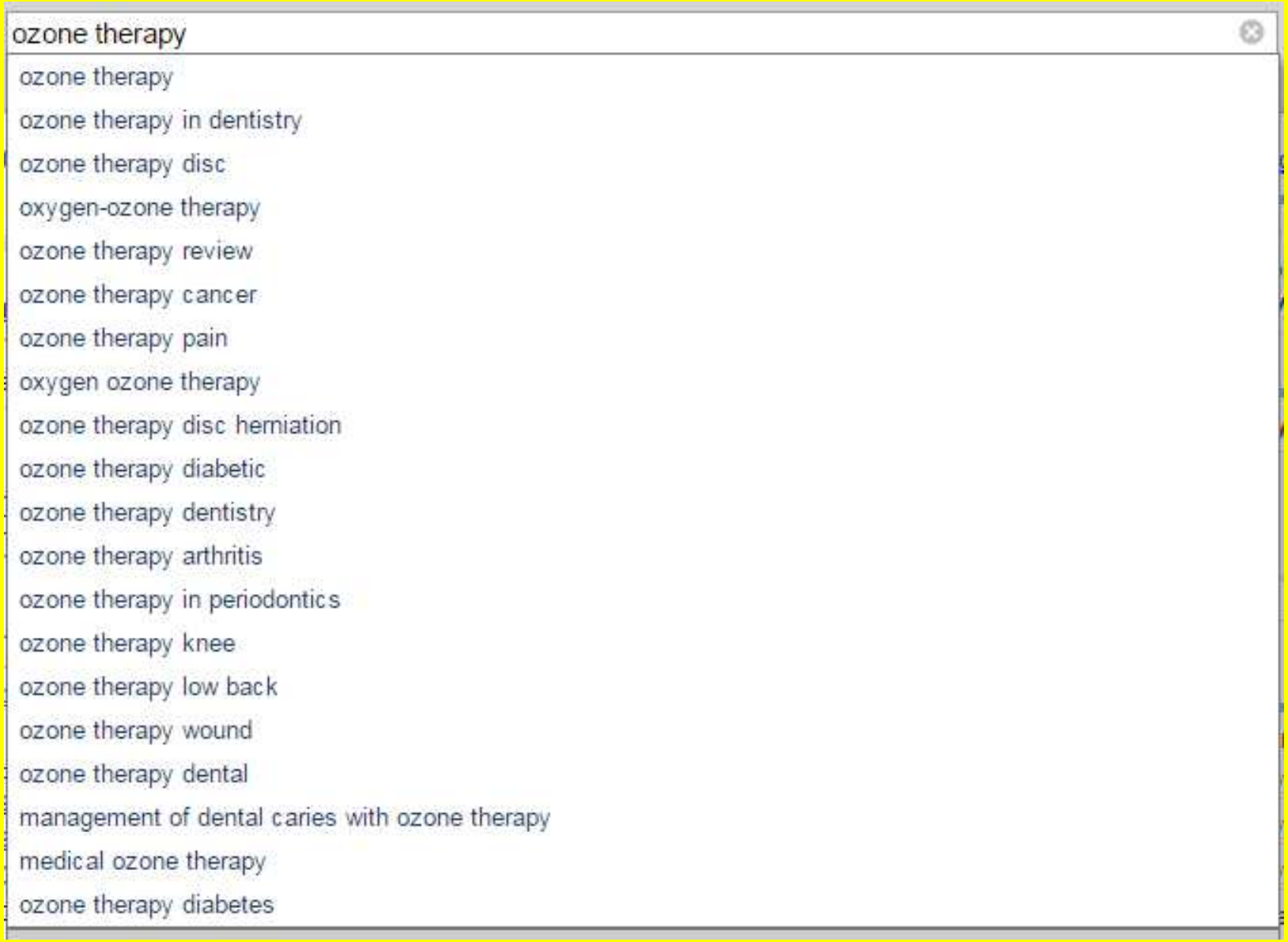
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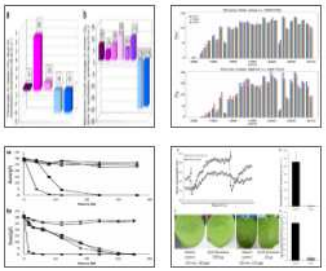

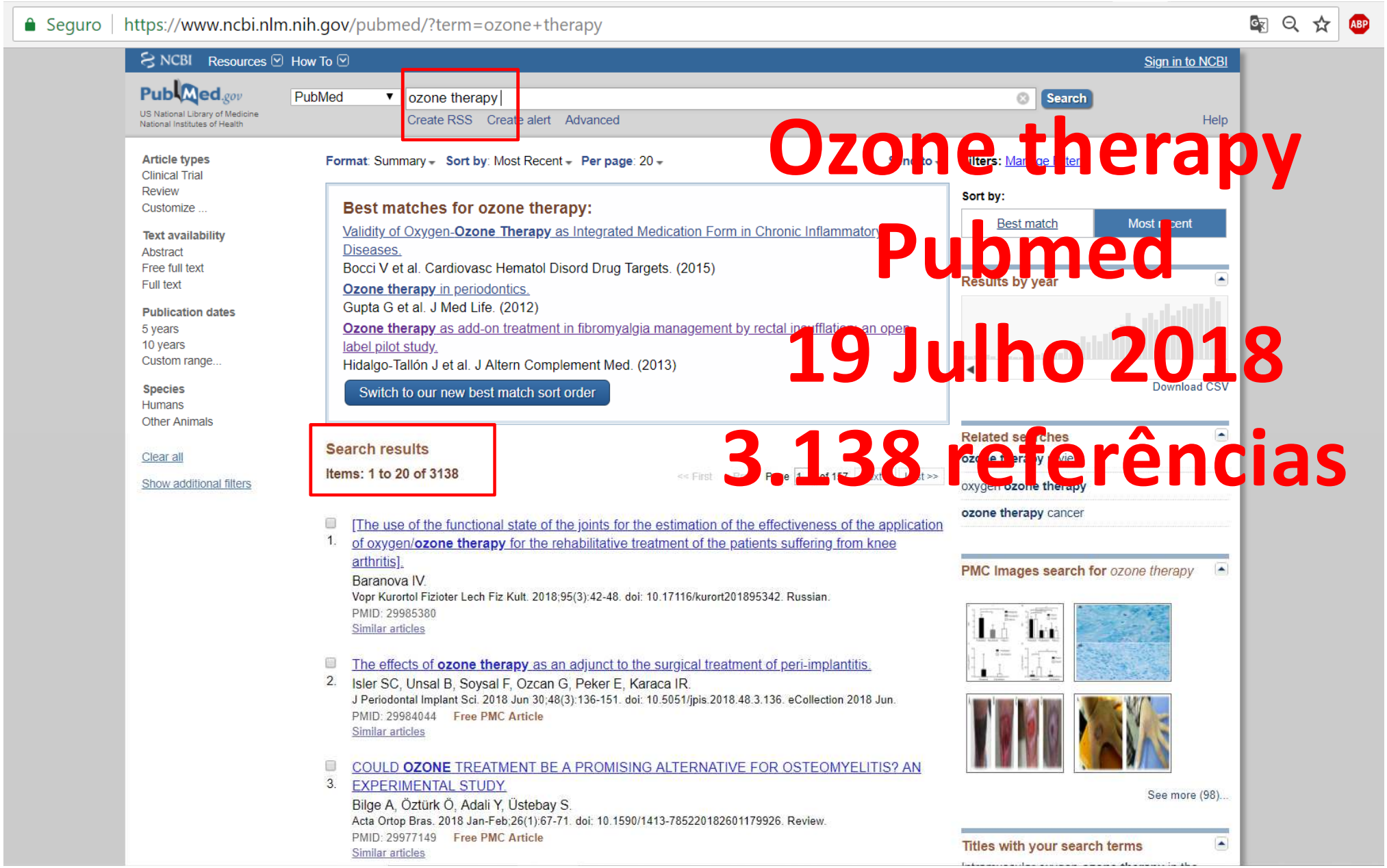
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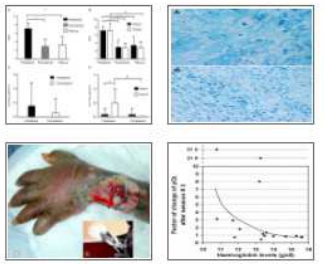

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Ozone therapy for the treatment of chronic wounds: A systematic review. [Int Wound J. 2018]

REVIEW

Ozone therapy: an overview of pharmacodynamics, current research, and clinical utility

Noel L. Smith[1], Anthony L. Wilson[2], Jason Gandhi[2, 3], Sohrab Vatsia[4], Sardar Ali Khan[2, 5, *]

1 Foley Plaza Medical, New York, NY, USA
2 Department of Physiology and Biophysics, Stony Brook University School of Medicine, Stony Brook, NY, USA
3 Medical Student Research Institute, St. George's University School of Medicine, Grenada, West Indies
4 Department of Cardiothoracic Surgery, Lenox Hill Hospital, New York, NY, USA
5 Department of Urology, Stony Brook University School of Medicine, Stony Brook, NY, USA
*Correspondence to: Sardar Ali Khan, M.D., skysalik@gmail.com.
orcid: 0000-0002-4759-530X (Sardar Ali Khan)

Abstract

The use of ozone (O_3) gas as a therapy in alternative medicine has attracted skepticism due to its unstable molecular structure. However, copious volumes of research have provided evidence that O_3's dynamic resonance structures facilitate physiological interactions useful in treating a myriad of pathologies. Specifically, O_3 therapy induces moderate oxidative stress when interacting with lipids. This interaction increases endogenous production of antioxidants, local perfusion, and oxygen delivery, as well as enhances immune responses. We have conducted a comprehensive review of O_3 therapy, investigating its contraindications, routes and concentrations of administration, mechanisms of action, disinfectant properties in various microorganisms, and its medicinal use in different pathologies. We explore the therapeutic value of O_3 in pathologies of the cardiovascular system, gastrointestinal tract, genitourinary system, central nervous system, head and neck, musculoskeletal, subcutaneous tissue, and peripheral vascular disease. Despite compelling evidence, further studies are essential to mark it as a viable and quintessential treatment option in medicine.

Key words: ozone; ozone therapy; ozone gas; autohemotherapy; oxidative stress; reactive oxidative species; lipid ozonation products; oxidative preconditioning

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Doenças Cardiovasculares

Additional Table 1: Cardiovascular indications for O_3 therapy

Study	Pathology	Concentration and route of O_3 administration	Type of study	Measured parameter(s)	Results	Side effect(s)	Mechanism of action
Martínez-Sánchez et al.[14]	Coronary artery disease	57 patients with massive cerebral infarction	Ungrouped; cocktail therapy: nimodipine (10 mg) intravenously, once per day, for 10 consecutive days	Prothrombin time	Significantly improved ($P < 0.001$)	None	Upregulation of adenosine A_2 receptor
				Oxidative stress levels	Increased antioxidant activity	None	Increased SOD and catalase enzyme activity
Hernandez et al.[40]	Previous myocardial infarction (3 months to 1 year)	200 mL of blood subjected to O_3-AHT, for a final concentration of 50 mg/L; treatment was given 5 days a week for up to 15 sessions	Pretest-posttest design ($n = 22$)	Serum lipid pattern	Cholesterol and low-density lipoprotein were significantly reduced with no changes in high-density lipoprotein and triglycerides	Not reported	Initiating radical formation which increasing lipid peroxidation
				Activity of antioxidant defense system	Biologically significant increases on erythrocyte GPx and glucose-6-phosphate dehydrogenase	Not reported	O_3-AHT stimulates ROS scavenger enzymes

Note: O_3: Ozone; O_2: oxygen; O_3-AHT: O_3 autohemotransfusion; GPx: glutathione peroxidase; SOD: superoxide dismutase; ROS: reactive oxidative species.

Lesões Cutâneas

Additional Table 2: Subcutaneous tissue indications for O_3 therapy

Study	Pathology	Concentration and route of O_3 administration	Type of study	Measured parameter(s)	Results	Side effect(s)	Mechanism of action
Wainstein et al.[41]	Diabetic foot ulcer	A noninvasive sealed chamber was used in two phases. Phase I delivered 96% O_2 and 4% O_3 (80 µg/mL) for up to 4 times a week for 4 weeks. Phase II delivered 98% O_2 and 2% O_3 (40 µg/mL) until the 12th week	Double-blind, randomized, placebo-controlled clinical trial ($n = 61$)	Wound closure	Of the patients completing per protocol, wound closure was significantly greater than controls ($P = 0.03$), expressly in patients with small ulcers initially (≤ 5 cm^2)	Control group ($n = 2$) O_3 group ($n = 5$); none of the adverse events were linked causally with the O_3 treatment used	Induced negative pressure by the device may enhance fluid removal and increase perfusion; O_3 bactericidal capabilities and a reduction of blood viscosity improves perfusion
Martinez-Sanchez et al.[42]	Diabetic foot ulcer	20 sessions of O_3 *via* rectal insufflation (50 mg/L) and local treatment (60 mg/L) *via* sealed bag with O_3	Randomized controlled clinical trial ($n = 101$)	Wound size	Significant decrease in area and perimeter	None	Activation of SOD, control of hyperglycemia, and decreased endothelial damage
				Glucose levels	Reduced hyperglycemia ($P < 0.05$)	None	Increased antioxidant properties allowing for increase in insulin sensitivity, facilitating increased glucose uptake
				Oxidative stress	Increased antioxidant enzyme defense	None	Increased SOD and catalase enzymes and activation of NF-κB *via* normalizing levels of H_2O_2
Elvis et al.[3]; Bertolotti et al.[43]; Moore et al.[44]	Buruli ulcer (*Mycobacterium ulcerans*)	Insufflation of a sealed bag with an O_3-O_2 mixture with an O_3 concentration of 30 µg/mL	Case study ($n = 1$)	Wound closure	No visible necrosis (with granulations) after the first week; ulcer was eventually eradicated (without granulations)	None	Oxidizes phospholipids and lipoproteins on the bacteria's cell envelope, thus attenuating its integrity, changing the permeability of the membrane. Lysis and cell death ensues
				Histological and PCR analysis	Absence of *M. ulcerans*		
Shah et al.[45]	Non-healing or ischemic wounds	Insufflation of a sealed bag O_3-O_2 (70 µg) mixture in conjunction with O_3-AHT (50 mL of blood with an O_3 concentration of 70 µg)	Case study ($n = 1$)	Regression of necrotic tissue	On the 5th day of treatment, necrosis regressed enough for surgeons to perform surgery, implementing a biological cover over the location of the previous non-healing wound	None	Attenuates bacterial cell walls *via* oxidation; stimulates formation of LOP, which acts on endothelium to release prostacyclin, IL-8 and NO, to increase vasodilation; ROS causes the release of TGF-β, IL-8, and PDGF *via* platelet aggregation to stimulate wound healing; O_3-AHT increases O_2 delivery and increase antioxidant enzymes to help reperfusion and avoid excessive inflammation

Note: O_3: Ozone; O_2: oxygen; SOD: superoxide dismutase; LOP: lipid ozonation products; IL-8: interleukin-8; NO: nitric oxide; ROS: reactive oxidative species; TGF-β: transforming growth factor beta; PDGF: platelet-derived growth factor; NF-κB: nuclear factor-kappa B; H_2O_2: hydrogen peroxide; O_3-AHT: O_3 autohemotransfusion.

Doenças Arteriais Periféricas

Additional Table 3: Peripheral vascular disease indications for O_3 therapy

Study	Pathology	Concentration and route of O_3 administration	Type of study	Measured parameter(s)	Results	Side effect(s)	Mechanism of action
Tafil-Klawe et al.[46]; Romero Valdes et al.[47]	Obliterative atheromatosis (without diabetes)	Normal saline with dissolved O_3 intravenously (500 mL with an O_3 60 µg/mL) and aerosol O_3 baths of lower extremities (O_3 concentration 19 µg/L)	Pretest-posttest design ($n = 64$)	Lysosomal hydrolase activity General condition	Lysosomal hydrolase activity returned to within normal limits Patients general condition improved	None reported	Improvement of blood supply to hypoxic areas to increase oxygen inflow *via* increases in 2,3-DPG. Immune cells have increased access to damaged tissue. Increased access allows for lysosomal enzymes to digest damaged cells. Increased antioxidant levels change the activity of lysosomal enzymes
Verrazzo et al.[48]	Peripheral occlusive arterial disease	O_3-AHT (32 µg/mL) every other day compared to HBOT	Randomly controlled trial ($n = 30$)	Blood viscosity Hct Erythrocyte filterability	Decrease in blood viscosity was present in O_3-AHT treatments compared to HBOT Unchanged Increased in O_3-AHT treatments compared to HBOT	None reported	Increase in plasma malonydialdehyde levels supports that O_3-derived free radicals increase. These are hypothesized to be selective for more rigid hematic cells, causing cell lysis. Selectively improving blood viscosity and filterability without decreasing Hct. Changes in fibrinogen and thrombin are seen to be transient effects of O_3-AHT
Giunta et al.[49]	Peripheral occlusive arterial disease	O_3-AHT (100 mL exposed to O_3 for 10 minutes)	Pretest-posttest design ($n = 27$)	Blood viscosity Oxygen delivery Erythrocyte filterability Hct Fibrinogen levels	Blood viscosity decreased Increase in oxygen delivery Erythrocyte filterability increased No significant change Plasma fibrinogen levels decreased	None reported	Increases oxidative stress and lipid peroxidation, contributing to selective cellular lysis of rigid erythrocytes. Additionally, lipid peroxidation of erythrocyte membranes alters pH, increasing oxygen unloading
Di Paolo et al.[50,51]	Peripheral artery disease	Extracorporeal blood oxygenation and ozonation (O_3 concentrations 40–100 µg/mL)	Randomly controlled study ($n = 28$)	Skin lesions, pain, improvement in quality of life	Significant regression of skin lesions, decreased pain, and increases sense of well-being	None	Stimulates cytokine secretion of leukocytes to digest cellular derbis build up and allows vasodilation *via* NO

Note: O_3: Ozone; O_2: oxygen; SOD: superoxide dismutase; LOP: lipid ozonation products; IL-8: interleukin-8; NO: nitric oxide; ROS: reactive oxidative species; TGF-β: transforming growth factor beta; PDGF: platelet-derived growth factor; NF-κB: nuclear factor-kappa B; H_2O_2: hydrogen peroxide; O_3-AHT: O_3 autohemotransfusion; HBOT: hyperbaric oxygen therapy; Hct: hematocrit.

Doenças Neurológicas

Additional Table 4: Neurological indications for O_3 therapy

Study	Pathology	Concentration and route of O_3 administration	Type of study	Measured parameter(s)	Results	Side effect(s)	Mechanism of action
Zanardi et al.[2]; Molinari et al.[52,53]; Lintas et al.[54]	Multiple sclerosis	240 g blood mixed with 180 mL O_2/O_3 (O_3 at 40 µg/mL) and re-injected; O_3-AHT	Pretest-posttest design (multiple case studies) ($n = 9$)	Cerebral oxygenation *via* near-infrared spectroscopy system and cyt c levels	Increased cyt c levels and oxygenation levels and increase in brain metabolism	None reported	O_3-AHT decreases oxidative stress *in vivo*, lowering mitochondrial damage and inflammation to reverse the impairments on cyt c seen in afflicted patients
Leon Fernandez et al.[30]; Clavo et al.[55]	Refractory headache	O_3-AHT (220–300 mL at a concentration between 30–60 µg/mL)	Case-control design ($n = 5$)	Number of headaches Pain intensity on the visual analog scale	Significantly decreased unchanged Significantly reduced	Ecchymosis at the site of injection	Induces regulation of cerebral blood flow and oxygen delivery to ischemic tissues, in part due to the increase 2,3-DPG in erythrocytes and release of NO by the endothelium, fostering a regulation of metabolism. Upregulation of cytokines from lymphocytes and increased antioxidant enzymes balance oxidation levels. O_3's enhancement of adenosine A_1 receptors provides evidence for its ability to act as a self-regulator of cortical electrical activity and neurotransmitters *via* reduction of glutamate release
Valacchi et al.[23]; Ajamieh et al.[32]; Clavo et al.[56,57]	Radiation-induced brain ischemia	O_3-AHT (300 mL at a concentration of 60 µg/mL of O_3/O_2)	Case-control design ($n = 7$) and case report ($n = 1$)	Cerebral blood flow	Improved after treatment	None reported	Induces ROS and LOP to stimulate NO, IL-8 release while inhibiting ET-1 and E-selectin, which could potentially improve cerebral blood flow. May also improve erythrocyte flexibility and blood rheology

Note: O_3: Ozone; O_2: oxygen; O_3-AHT: O_3 autohemotransfusion; cyt c: cytochrome-c; ROS: reactive oxidative species; LOP: lipid ozonation products; 2,3-DPG: 2,3-diphosphoglycerate; NO: nitric oxide; IL-8: interleukin-8; ET-1: endothelin 1.

Patologias de Cabeça e Pescoço

Additional Table 5: Head and neck indications for O_3 therapy

Study	Pathology	Concentration and route of O_3 administration	Type of study	Measured parameter(s)	Results	Side effect(s)	Mechanism of action
Bocci et al.[58]; Ragab et al.[59]	Sensorineural hearing loss	O_3-AHT (100 mL of blood with a 1:1 gaseous mixture O_2-O_3)	Randomized controlled trial (n = 45)	Multiple methods assessing hearing outcomes (mean hearing gain, PTA, SRT, and subjective recovery rates)	All improved significantly with O_3 compared to placebo	None	Multifaceted stimulation of cellular metabolism and increase of erythrocyte activity, which increases 2,3-DPG, may attenuate cellular stress. Shift in the oxyhemoglobin dissociation curve and an increase NO allows for increase oxygen supply to tissues of hypoxia in the inner ear
Clavo et al.[60]	Head and neck tumors	O_3-AHT (60 µg/mL) and rectal insufflation (60 µg/mL)	Controlled case study (n = 19)	Patient outcome	No significant difference in overall survival between O_3 and traditional treatment	Transient meteorism and constipation	Increased production of 2,3-DPG in RBCs *via* increase of malondialdehyde and lipid peroxidation, allowing for a shift in the oxyhemoglobin dissociation curve to increase unloading of O_2 to tissues. Changes in RBC cell membranes *via* addition/removal of charges allows for increased membrane flexibility and decreased blood viscosity. Thus, with an added tissue perfusion, increased oxygenation, and increased antioxidant levels, O_3 is suspected to be a pivotal adjunct therapy
Clavo et al.[60,61]		O_3-AHT (60 µg/mL)	Controlled case study (n = 14)	Levels of oxygenation (hypoxic values, tumor pO_2, and [Hb])	All improved with O_3 therapy	None	
Menéndez et al.[62]	Vestibulocochlear syndrome	Paravertebral O_3 injection at C2-3 vertebrae (8 mg/L, flow of 60 mL/min)	Pretest-posttest design (n = 50)	Tinnitus	Improved by 65%	None reported	Increases in SOD, GSH, GPx, and CAT levels, while observing low lipid peroxidation provides evidence that O_3 helps balance cellular redox. The cellular redox balance may improve symptoms of these syndromes
				O_2 delivery	Increase in O_2 delivery		
				Nystagmus	Improved by 100%		
				Vertigo	Improved by 90%		
				Hearing loss	Improved by 80%		
Borrelli et al.[63]	Dry form of AMD	O_3-AHT (200 mL of blood with a total O_3 does equivalent to 4.0 mg)	Two clinical studies (n = 217)	Progression of disease	Stops progression	None	Improves blood rheology, glycolytic metabolism in RBCs that can increase O_2 delivery *via* increased ATP and 2,3-DPG, increase NO and vasodilation, release growth factors, and have an increase of antioxidant enzymes that can minimize the death of photoreceptors seen in dry AMD
				Visual acuity	Significantly improved		

Note: O_3: Ozone; O_2: oxygen; O_3-AHT: O_3 autohemotransfusion; AMD: age-related macular degeneration; 2,3-DPG: 2,3-diphosphoglycerate; RBC: red blood cell; SOD: superoxide dismutase; GPx: glutathione peroxidase; GSH: glutathione; PTA: pure-tone average; SRT: speech reception threshold; CAT: catalase; NO: nitric oxide; pO_2: partial pressure of oxygen; Hb: hemoglobin.

Patologias Ortopédicas

Additional Table 6: Orthopedic indications for O_3 therapy

Study	Pathology	Concentration and route of O_3 administration	Type of study	Measured parameter(s)	Results	Side effect(s)	Mechanism of action
Steppan et al.[64]; Paoloni et al.[65]; Oder et al.[66]; Magalhaes et al.[67]	Herniated lumbar discs	Intradiscal and extradiscal injection (1–3 mL O_2/O_3)	Meta-analysis (n = 12)	Meta-analysis for pain levels (visual analog scale)	Significant mean improvement of 3.9	Significantly low complication rate (0.064%)	Redox capabilities allow proteoglycans in the nucleus pulposus to be oxidized, leading to a small decrease in volume of the nucleus pulposus. Decreased volume decreases pressure and attenuates pain. O_3's anti-inflammatory effects due to the redox properties are also speculated to have analgesic effects. O_3's disinfectant properties are beneficial when using intra- and extradiscal injections because it lessens the risk of infection
				Meta-analysis for functionality (ODI)	Significant mean improvement of 25.7		
				Meta-analysis for functionality (modified MacNab)	Likelihood of showing improvement was 79.7%		
Al-Jaziri et al.[68]	Spine and joint osteoarthritis	Intra-articular and paravertebral muscle injections (20 μg/mL)	Prospective study (n = 220)	Pain level after 4, 8, and 12 sessions	Significantly decrease (P = 0.005, P = 0.005, P = 0.0043, respectively)	None	Ability to activate enzymes catalyzing peroxide reactions allowing for protection against ROS and peroxides. O_3's anti-inflammatory, analgesic effects, and anti-oxidative effects, taken together with the significantly decreased pain levels long-term, allows for speculation on possible histological changes after using O_3 therapy
				Follow-up pain levels (mean follow-up time is ~10 months)	Significantly decrease (P = 0.0048)		
Bonetti et al.[69]	First degree spondylolisthesis and spondylolysis	CT-guided bilateral perignglionic infiltration of O_2-O_3 and O_2-O_3 injection into lysis point of neural arch ¾ mL O_2-O_3 gas mixture at 25 μg/mL)	Prospective study (n = 18)	Pain levels after treatments using modified MacNab	15 patients (83.3%) had complete remission of pain. 3 patients (16.7%) had poor levels of improvement	None	By injection, the gas mixture directly proximal to the lysis points allows for analgesic and anti-inflammatory actions on the meningeal branches of a spinal nerve. Also, prostaglandin and cytokine levels are balanced because of O_3's ability to increase SOD production and to reduce ROS. Local improvement in circulation after treatment allows for increased eutrophic delivery
				Pain levels at 1-month follow-up using modified MacNab	15 patients (83.3%) had complete remission of pain. 3 patients (16.7%) had poor levels of improvement		
				Pain levels at 3-month follow up using modified MacNab	13 patients (72.2%) had complete remission of pain. 2 patients (11.1%) had satisfactory levels of improvement of pain. 3 (16.7%) patients had poor levels of improvement		
				Pain levels at 3-month follow up using modified MacNab	13 patients (72.2%) had complete remission of pain. 2 patients (11.1%) had satisfactory levels of improvement of pain. 3 patients (16.7%) had poor levels of improvement		

Note: O_3: Ozone; O_2: oxygen; ODI: Oswestry Disability Index; CT: computed tomography; ROS: reactive oxidative species; SOD: superoxide dismutase.

Doenças Gastrointestinais

Additional Table 7: Gastrointestinal indications for O_3 therapy

Study	Pathology	Concentration and route of O_3 administration	Type of study	Measured parameter(s)	Results	Side effect(s)	Mechanism of action
Zanardi et al.[2]; Bocci et al.[5,27,70]; Zaky et al.[71]	Chronic hepatitis C	O_3-AHT (150 mL with a concentration of 25% O_2/O_3 raised by 5% every week for 5 weeks) and rectal O_3 insufflation (300 mL at 40% O_3/O_2	Case-control design (n = 52)	Presenting symptom progression (7 clinical symptoms assessed)	Significantly improved symptoms	None reported	Uses peroxidation to damage the viral capsid and disrupts the reproductive cycle of viruses by dismantling virus-to-cell contact. Formation of peroxides from O_3 stimulates the release of leukocytes and cytokines. Decreased viral load fosters liver enzymes replenishment and improved liver function
				ALT and AST	Normalized significantly more than conventional therapy		
				PCR analysis for HCV RNA	Disappearance of HCV RNA in 25% of O_3-AHT patients after 30 sessions and 44.4% after 60 sessions		
Zaky et al.[72]	Liver cirrhosis	Rectal O_3 insufflation (12 sessions, 300 mL at 40% O_3) as an adjunct to propranolol	Case-control design (n = 15)	Propranolol clearance	Increased elimination of propranolol	None reported	Propranolol metabolism is carried out by an oxidative enzyme in the CYP family, which is contingent on oxygenation. Increased portal vein oxygenation reported in the study would, therefore, optimize propranolol metabolism. This perfusion is forested by the release of mediators of NO
				Liver function tests	Significant reduction in prothrombin time		
				Portal vein oxygenation	Significantly increased after rectal insufflation of O_3		
Peretyagin et al.[74]	Gastrointestinal tract ulcers	O_3 therapy courses *via* intragastral, intravenous, biopuncture, cutaneous routes (200 mL at 3 mg/L of O_3)	Case-control design (n = 71)	Clinical symptoms (assessment of 6)	Significantly improved	In treatment group (n = 34), 1 participant had skin itch, 4 had sickness, 2 vomited and 5 had constipation. However, all of these were significantly lower than the control group	Decreases ischemia in developing ulcers and activates the immune response to increase recovery of persistent ulcers

Note: O_3: Ozone; O_2: oxygen; O_3-AHT: O_3 autohemotransfusion; CTCAE: common terminology for adverse events; AST: aspartate aminotransferase; ALT: alanine aminotransferase; HCV: hepatitis C virus; CYP: cytochrome P450; NO: nitric oxide.

Patologias Genito-urinárias

Additional Table 8: Genitourinary indications for O_3 therapy

Study	Pathology	Concentration and route of O_3 administration	Type of study	Measured parameter(s)	Results	Side effect(s)	Mechanism of action
Neimark et al.[75]; Gu et al.[76]	Chronic cystitis	Ozonated saline (1,000 µg/L)	Controlled clinical trial ($n = 65$)	Laser Doppler flowmetry used to determine perfusion	Significantly increased, close to control levels	None reported	Microcirculation and structural reorganization of the bladder mucosa
				Cystoscopy with biopsy of the bladder mucosa	More positive shifts in hyperemia and edema then standard treatment alone		
				PRA	Significantly decreased		
				Ang II	Significantly decreased		
				ALD	Significantly decreased		
Gu et al.[76]; Clavo et al.[77]	Renal complications secondary to hepatitis	O_3-AHT (100 mL, 35 µg/mL)	Randomly controlled trial ($n = 85$)	Renal blood flow	Significantly increased with O_3 therapy compared to control	No obvious side effects were seen	Increased oxygen carrying and releasing capacity of Hb, can activate metabolism in RBCs, and improve microcirculation to the liver and kidney. O_3's activation of the immune and free radical removal systems can reduce the work load of the liver while improving immune response to viruses. By improving the oxygen and blood supply to the kidney, there is a decrease in PRA, Ang II, ALD caused by hepatitis, thus reducing renal damage
					Damage to renal function	Seen in lower proportion with O_3 therapy	
					Survival rate	Significantly higher proportion survived with O_3 treatment compared to control	
					Presence of hematuria	Post-1-week macroscopic hematuria disappeared. Post-8 weeks, microscopy showed about 10 RBCs/microscopic field. After 6 months, there was no evidence of macroscopic hematuria	
					Hb levels	After week 2, Hb concentration increased by 0.5 g/dL per week	
Clavo et al.[77]; Bonforte et al.[78]	Radiation-induced cystitis with hematuria	Intravesical instillation of ozonated water (35 µg/mL)	Case study ($n = 1$)	Cystoscopy	After week 3, significant improvement was seen	Soft bladder pruritus after initial sessions	Local and transient increase in oxidative stress causes an increase in synthesis of antioxidants, thus increase protection against free-radical tissue damage. O_3 can also increase local repair mechanisms, affecting hematological parameters and increasing tissue oxygenation
					Presence of bacteria causing UTI	Regression of bacteria and UTI symptoms	
Bonforte et al.[78]	UTI	Ozonated saline catheter injection into urinary bladder	Case series report ($n = 3$)	Presence of bacteria	Decreased presence of bacteria	None	Antiseptic ability *via* lipid peroxidation, DNA damage and cell death, in addition to its immune system stimulation may account for its ability to combat bacterial UTIs

Note: O_3: Ozone; O_3-AHT: O_3 autohemotransfusion; UTI: urinary tract infection; PRA: plasma renin activity; Ang II: angiotensin II; ALD: aldosterone; Hb: hemoglobin; RBC: red blood cell.

ORIGINAL CONTRIBUTION

Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines

Context The joint cardiovascular practice guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA) have become important documents for guiding cardiology practice and establishing benchmarks for quality of care.

Objective To describe the evolution of recommendations in ACC/AHA cardiovascular guidelines and the distribution of recommendations across classes of recommendations and levels of evidence.

Data Sources and Study Selection Data from all ACC/AHA practice guidelines issued from 1984 to September 2008 were abstracted by personnel in the ACC Science and Quality Division. Fifty-three guidelines on 22 topics, including a total of 7196 recommendations, were abstracted.

Data Extraction The number of recommendations and the distribution of classes of recommendation (I, II, and III) and levels of evidence (A, B, and C) were determined. The subset of guidelines that were current as of September 2008 was evaluated to describe changes in recommendations between the first and current versions as well as patterns in levels of evidence used in the current versions.

Results Among guidelines with at least 1 revision or update by September 2008, the number of recommendations increased from 1330 to 1973 (+48%) from the first to the current version, with the largest increase observed in use of class II recommendations. Considering the 16 current guidelines reporting levels of evidence, only 314 recommendations of 2711 total are classified as level of evidence A (median, 11%), whereas 1246 (median, 48%) are level of evidence C. Level of evidence significantly varies across categories of guidelines (disease, intervention, or diagnostic) and across individual guidelines. Recommendations with level of evidence A are mostly concentrated in class I, but only 245 of 1305 class I recommendations have level of evidence A (median, 19%).

Conclusions Recommendations issued in current ACC/AHA clinical practice guidelines are largely developed from lower levels of evidence or expert opinion. The proportion of recommendations for which there is no conclusive evidence is also growing. These findings highlight the need to improve the process of writing guidelines and to expand the evidence base from which clinical practice guidelines are derived.

JAMA. 2009;301(8):831-841 www.jama.com

A

• Level of evidence A: recommendation based on evidence from multiple randomized trials or meta-analyses

11 %

Cardiologia

C

• Level of evidence C: recommendation based on expert opinion, case studies, or standards of care.

48 %

Foi realizada uma ampla pesquisa bibliográfica na Biblioteca Virtual em Saúde (BVS) e no PubMed no dia 09 de agosto de 2018, com os termos de busca representando o assunto **Ozonioterapia**.

Na BVS, o resultado da pesquisa recuperou 1.108 citações de estudos científicos e técnicos (figura 1) das bases de dados Medline, LILACS e outras, e no PubMed o resultado da pesquisa recuperou 1.535 citações (figura 2).

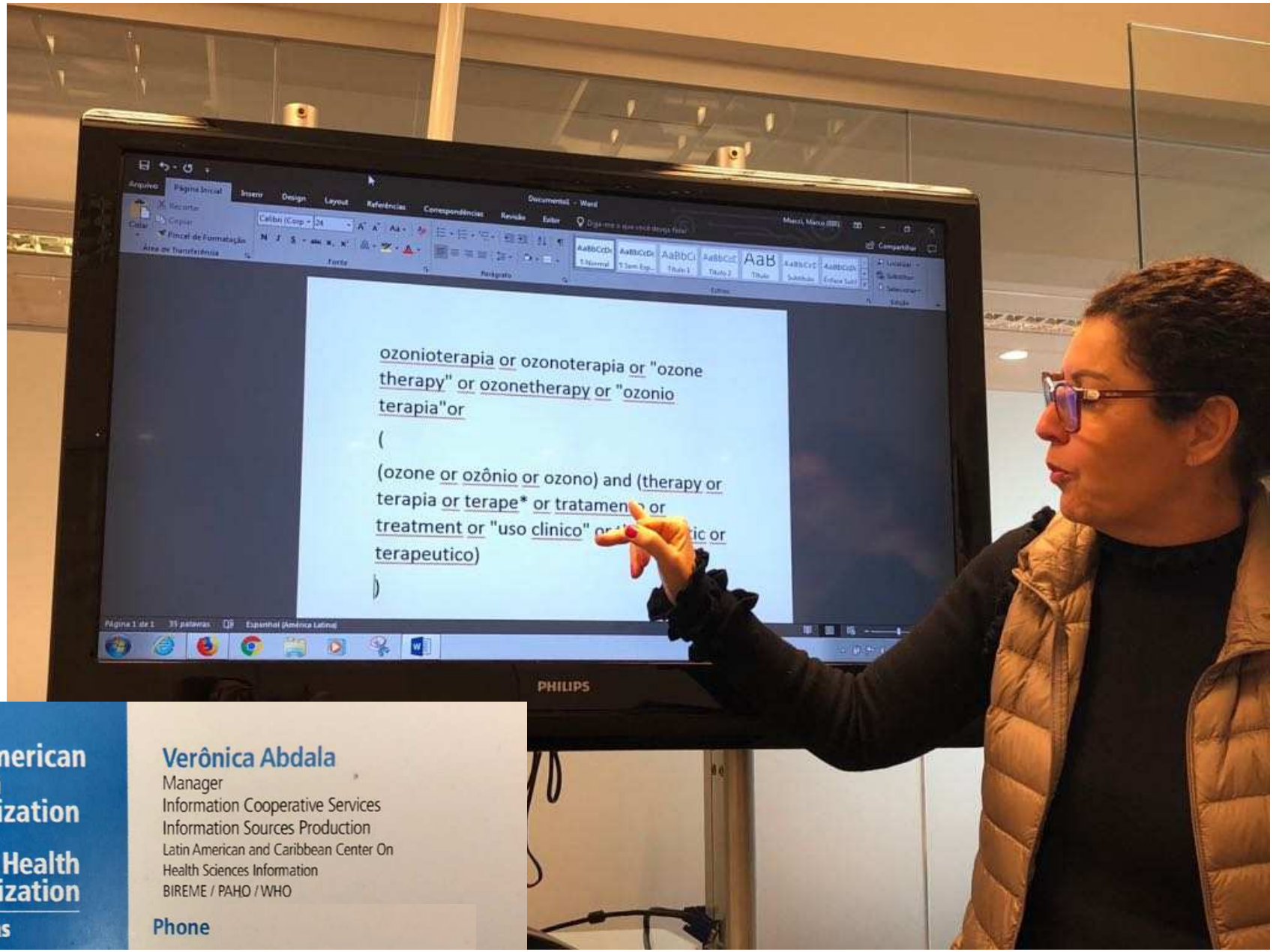
Juntando os resultados da pesquisa na BVS e PubMed, excluindo os estudos duplicados, foram selecionados 147 Ensaios Clínicos Randomizados e 12 Revisões Sistemáticas.

RBBD

Entrevista

Os rumos da comunicação científica na área da saúde

Carmen Verônica Mendes Abdala é bibliotecária e trabalha na BIREME desde 1991. Atualmente é responsável pela área de serviços e fontes de informação. Sua larga experiência em gestão de redes e bibliotecas virtuais é reconhecida em todo Brasil e nos países da América Latina, Europa e África. Sua habilidade com o tema de acesso à informação nos alertou para a relevância de um bate-papo com Verônica. Com a simpatia e cortesia, que lhe são peculiares, atendeu nosso pedido e conversou conosco.



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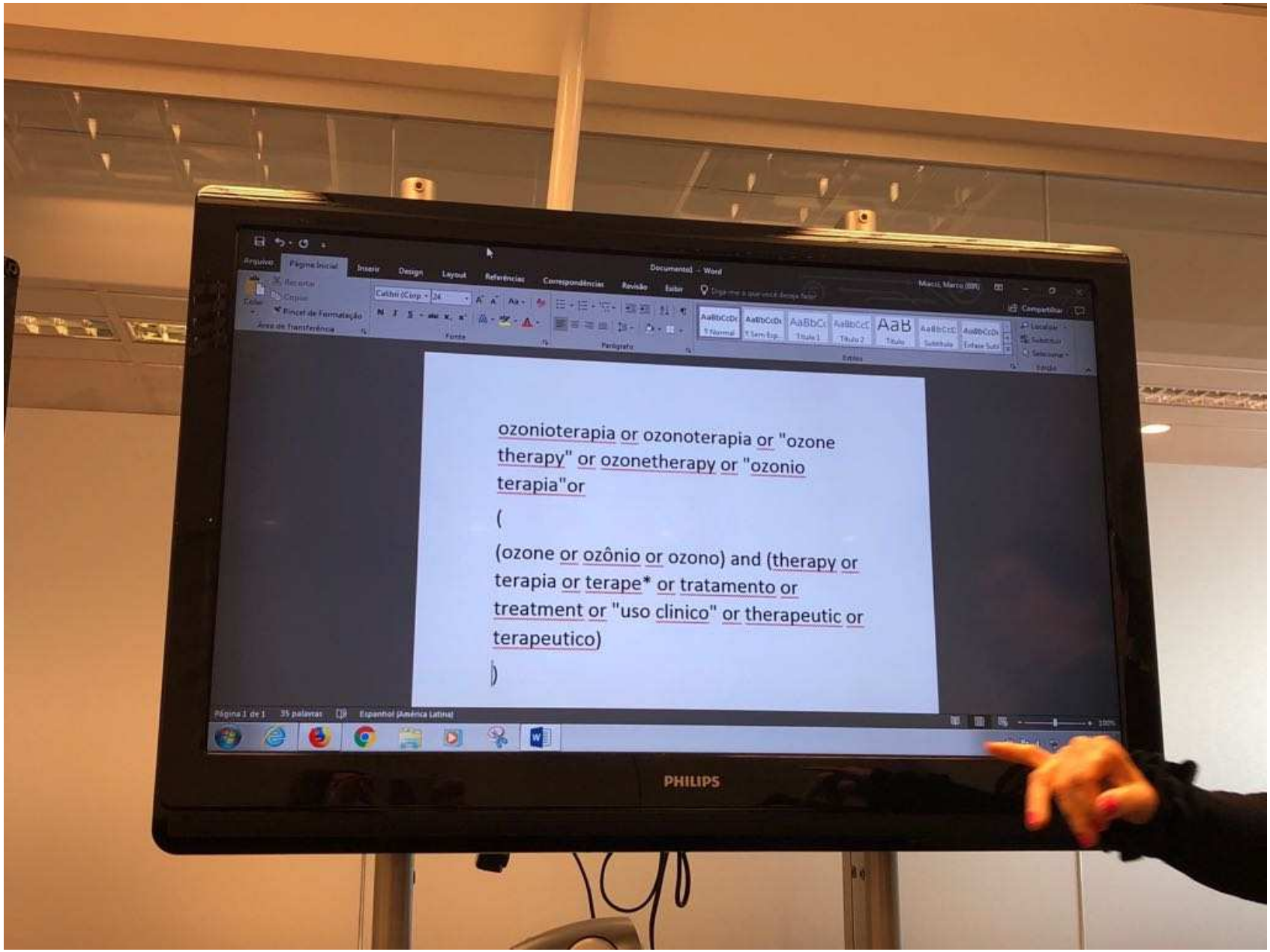
Verônica Abdala
Manager
Information Cooperative Services
Information Sources Production
Latin American and Caribbean Center On Health Sciences Information
BIREME / PAHO / WHO

Phone


ozonioterapia or ozonoterapia or "ozone therapy" or ozonetherapy or "ozonio terapia"or
(
(ozone or ozônio or ozono) and (therapy or terapia or terape* or tratamento or treatment or "uso clinico" or therapeutic or terapeutico)
)
PHILIPS

Detalhe da pesquisa sobre Ozonioterapia na BVS – www.bvsalud.org em 09/agosto/2018, que recuperou 1.108 citações com a seguinte expressão de busca:

Search #1 –

MH:"ozonio/uso terapeutico" or MH:"ozonio/administracao e dosagem"

Search #2 –

TW:(ozonioterapia or ozonoterapia or "ozone therapy" or ozonetherapy or "ozonio terapia" or (ozon* (hidrozonot* or balneoterap*)))

Search #3 –

Ti:((ozone or ozonio or ozono or ozonat* or ozoniz*) and TW:(therapy or terapia or terape* or TW:((tratamento or treatment) and not (water or agua or wastewater*)) or TW:"uso clinico" or TW:therapeutic or TW:terapeutico))

Search #4 –

(esgotos or "purificacao da agua" or "poluentes atmosfericos" or "Poluentes Químicos da Água" or "oxidantes fotoquimicos" or "eliminacao de residuos" or "poluicao do ar" or ((water or agua or wastwat*) (treatment or tratamento)) or "Dióxido de Carbono" OR "Clima" OR "Radonio" or radon OR "Folhas de Planta" OR "Luz Solar" OR "Fotossíntese" OR "Populus" OR "Triticum" OR "Feijão de Soja" OR "Betula" OR "Atmosfera" OR "Ar" OR "Ecossistema" OR "Altitude" OR "Árvores" OR "Hemiterpenos" OR "Proteínas de Plantas" OR "Plantas" OR "Clorofila" OR "Pentanos" OR "Oryza" OR "Estações do Ano" OR "Protetores Solares" or ethanol or industr* or etanol or "Waste Disposal, Fluid" OR "Water Purification" OR "Water Pollutants, Chemical" OR Sewage OR "Soil Pollutants" OR "Industrial Waste" or climate or "Ozônio Estratosférico" or "Stratospheric Ozone" or "Ozono Estratosférico" or "camada de ozonio" or ozonosfera or mh:Water OR "Water Microbiology" OR "Water Purification" OR "Hot Temperature" or "Air Pollutants" OR "Water Pollutants, Chemical" OR "Waste Disposal, Fluid" or "grain products" or "in-vitro" or "in vitro" or db:("SOF" OR "DECS" OR "LIS" OR "PAHO"))

Search #5 –

(#1 OR #2 OR #3) AND NOT #4

(MH:"ozonio/tu" or MH:"ozonio/ad" OR ozonioterapia or ozonoterapia or "ozone therapy" or ozonetherapy or "ozonio terapia" or (ozon* (hidrozonot* or balneoterap*)) OR Ti:((ozone or ozonio or ozono or ozonat* or ozoniz*) and (therapy or terapia or terape* or ((tratamento or treatment) and not (water or agua or wastewater*)) or "uso clinico" or therapeutic or terapeutico))) and not (esgotos or "purificacao da agua" or "poluentes atmosfericos" or "Poluentes Químicos da Água" or "oxidantes fotoquimicos" or "eliminacao de residuos" or "poluicao do ar" or ((water or agua or wastwat*) (treatment or tratamento)) or "Dióxido de Carbono" OR "Clima" OR "Radonio" or radon OR "Folhas de Planta" OR "Luz Solar" OR "Fotossíntese" OR "Populus" OR "Triticum" OR "Feijão de Soja" OR "Betula" OR "Atmosfera" OR "Ar" OR "Ecossistema" OR "Altitude" OR "Árvores" OR "Hemiterpenos" OR "Proteínas de Plantas" OR "Plantas" OR "Clorofila" OR "Pentanos" OR "Oryza" OR "Estações do Ano" OR "Protetores Solares" or ethanol or industr* or etanol or "Waste Disposal, Fluid" OR "Water Purification" OR "Water Pollutants, Chemical" OR Sewage OR "Soil Pollutants" OR "Industrial Waste" or climate or "Ozônio Estratosférico" or "Stratospheric Ozone" or "Ozono Estratosférico" or "camada de ozonio" or ozonosfera or mh:Water OR "Water Microbiology" OR "Water Purification" OR "Hot Temperature" or "Air Pollutants" OR "Water Pollutants, Chemical" OR "Waste Disposal, Fluid" or "grain products" or "in-vitro" or "in vitro" or db:("SOF" OR "DECS" OR "LIS" OR "PAHO"))

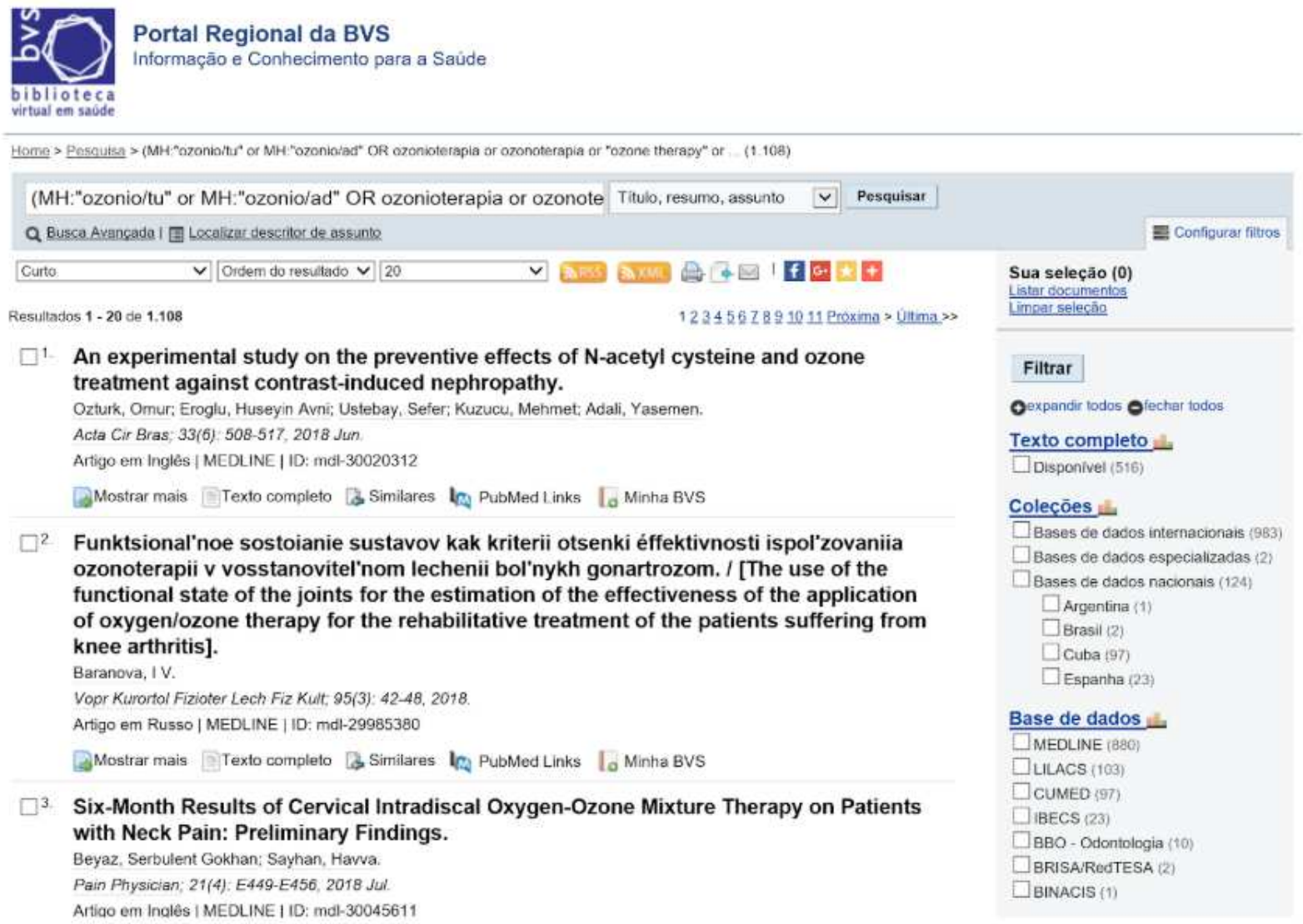


Figura 1 – Primeira página do resultado da pesquisa na BVS, em 9 de agosto de 2018.

Detalhe da pesquisa sobre Ozonioterapia no PubMed, em 9/agosto/2018, que recuperou 1.535 citações com a seguinte expressão de busca:

Search #1

ozone/tu[MH] OR ozone/ad[MH] OR "ozone therapy" OR "ozone bath therapy" OR ((Balneotherapy OR bath*) ozone*)

Search #2

(pollution OR mh:Water OR "Water Microbiology" OR "Water Purification" OR "Hot Temperature" OR "Air Pollutants" OR "Water Pollutants, Chemical" OR "Waste Disposal, Fluid" OR "grain products" OR "in-vitro" OR "in vitro")

Search #3

#1 NOT #2

ozone/tu[MH] OR ozone/ad[MH] OR "ozone therapy" OR "ozone bath therapy" OR ((Balneotherapy OR bath*) ozone*) NOT (pollution OR mh:Water OR "Water Microbiology" OR "Water Purification" OR "Hot Temperature" OR "Air Pollutants" OR "Water Pollutants, Chemical" OR "Waste Disposal, Fluid" OR "grain products" OR "in-vitro" OR "in vitro")

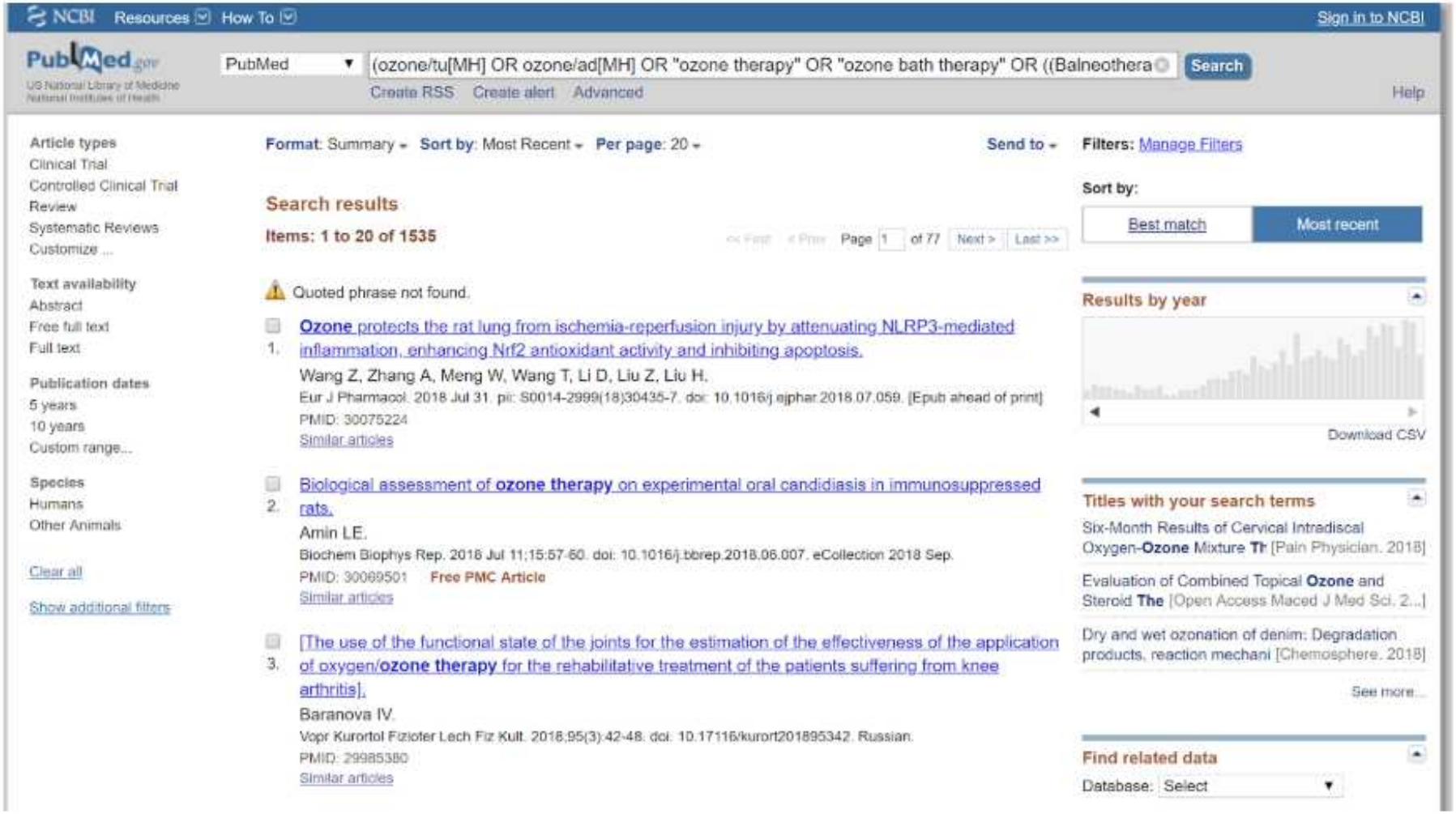


Figura 2 – Primeira página do resultado da pesquisa no Pubmed, em 9 de agosto de 2018.

Ensaios Clínicos Controlados

Clinical Trials

Revisões Sistemáticas

Ensaios Clínicos Controlados

Doenças Cardiovasculares

Additional Table 1: Cardiovascular indications for O_3 therapy							
Study	Pathology	Concentration and route of O_3 administration	Type of study	Measured parameter(s)	Results	Side effect(s)	Mechanism of action

0

Lesões Cutâneas

Additional Table 2: Subcutaneous tissue indications for O3 therapy

	Study	Pathology	Concentration and route of O3 administration	Type of study	Measured parameter(s)	Results	Side effect(s)	Mechanism of action
1.	ZHANG, Jing et al. Increased growth factors play a role in wound healing promoted by noninvasive oxygen-ozone therapy in diabetic patients with foot ulcers. **Oxidative medicine and cellular longevity**, v. 2014, 2014.	Diabetic Foot Ulcers (DFUs)	Ozone group treated by standard therapy plus oxygen-ozone treatment	Type 2 diabetic patients complicated with DFUs, stage 2~4, were randomized into control group treated by standard therapy only and ozone group treated by standard therapy plus oxygen-ozone treatment (n=50)	Wound sizes were measured; Tissue biopsies; Expressions of vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β) and platelet-derived growth factor (PDGF) were evaluated	The effective rate of ozone group was significantly higher than that of control group (92% versus 64%). The wound size reduction was significantly more in ozone group than in control group	Not reported	Ozone therapy promotes the wound healing of DFUs via potential induction of VEGF, TGF-β, and PDGF at early stage of the treatment.
2.	WAINSTEIN, Julio et al. Efficacy of ozone–oxygen therapy for the treatment of diabetic foot ulcers. **Diabetes technology & therapeutics**, v. 13, n. 12, p. 1255-1260, 2011.	Diabetic Foot Ulcers	Phase 1: Treatment sessions four times each week for the maximum period of 4 weeks. Gas concentrations were 96% oxygen and 4% (80 lg/mL) ozone. Phase 2: session frequency was reduced to twice a week to complete the 12 weeks of treatment, and gas concentration was changed to 98% oxygen and 2% (40 lg/mL) ozone.	Double-blind, randomized, placebo-controlled clinical trial (n=61)	Complete wound closure	Among the 34 subjects who completed the study per protocol (PP) (16 in the ozone group, 18 in the placebo group), a significantly higher rate of complete wound closure was observed in the ozone group (81% vs. 44%). Among PP patients with wound size 5 cm2, the rate of total wound closure was 100% versus 50% in the sham treatment group. Among PP patients, ozone treatment in addition to conventional treatment was superior to conventional treatment alone in promoting the complete healing of diabetic foot ulcers	Not reported	Extracted from abstract

Úlceras de Pé Diabético

DIABETES TECHNOLOGY & THERAPEUTICS
Volume 13, Number 11, 2011

DOI: 10.1089/dia.2011.0018

Original Article

Efficacy of Ozone–Oxygen Therapy for the Treatment of Diabetic Foot Ulcers

Julio Wainstein, M.D.,[1] Ze'ev Feldbrin, M.D.,[2] Mona Boaz, Ph.D.,[3] and Ilana Harman-Boehm, M.D.[4]

Abstract

Background: Diabetic foot ulcers are associated with significant morbidity. Conventional treatment modalities are often of limited success in promoting complete wound closure. The aim of the present study was to examine the efficacy of noninvasive ozone–oxygen therapy in the treatment of diabetic foot ulcers.

Methods: Diabetes patients with a Wagner classification stage 2 or 3 ulcer or a stage 4 ulcer after debridement of at least 8 weeks in duration were included in this double-blind, randomized, placebo-controlled clinical trial. Patients received conventional treatment in combination with either ozone–oxygen treatment or sham treatments for 12 weeks, and after an additional 12 weeks, wound status was re-examined.

Results: In total, 61 patients (62% male, 62.6±9.8 years old) participated in the study; 32 were randomized to ozone treatment, and 29 to placebo. The proportion of subjects with full wound closure did not differ significantly by treatment assignment (41% vs. 33%, $P=0.34$). Among the 34 subjects who completed the study per protocol (PP) (16 in the ozone group, 18 in the placebo group), a significantly higher rate of complete wound closure was observed in the ozone group (81% vs. 44%, $P=0.03$). Among PP patients with wound size $\leq 5\,cm^2$, the rate of total wound closure was 100% versus 50% in the sham treatment group ($P=0.006$). A nonsignificant, 55.5% relative increase in healed wound area was detected in the ozone group versus the placebo group ($4.2\pm4.9\,cm^2$ vs. $2.7\pm1.5\,cm^2$, $P=0.23$).

Conclusions: Among PP patients, ozone treatment in addition to conventional treatment was superior to conventional treatment alone in promoting the complete healing of diabetic foot ulcers.

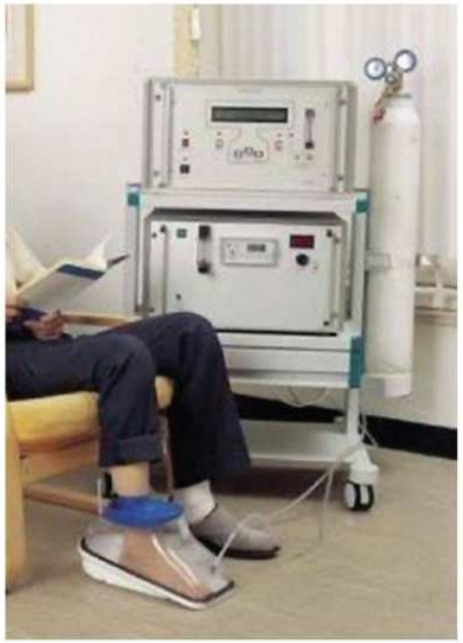


FIG. 1. The Ozoter 101 device. Color images available online at www.liebertonline.com/dia

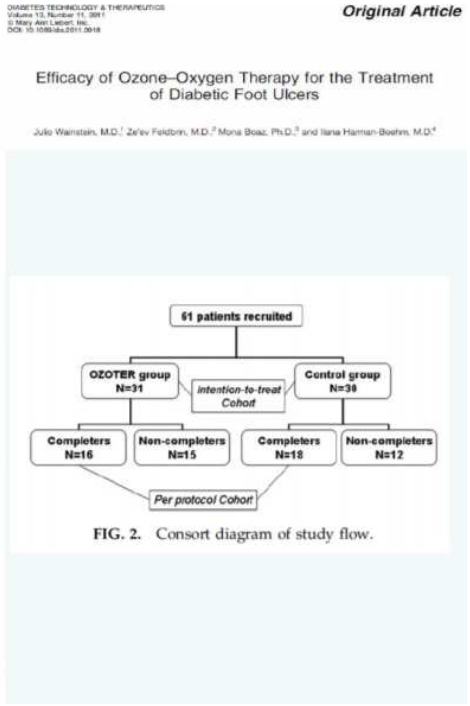


FIG. 2. Consort diagram of study flow.

Lesões Cutâneas

Additional Table 2: Subcutaneous tissue indications for O_3 therapy

	Study	Pathology	Concentration and route of O_3 administration	Type of study	Measured parameter(s)	Results	Side effect(s)	Mechanism of action
3.	ZAGIROV, U. Z.; ISAEV, U. M.; SALIKHOV, M. A. Clinicopathologic basis of ozonomagnetophoresis in treatment of festering wounds. **Khirurgiia**, n. 12, p. 24-26, 2008.	Festering wounds	Group 1: wound irrigation with ozone Group 2: ozone therapy was carried out in combination with low-frequency magnetic fields-ozonomagnetophoresis	Randomized Controlled Trial, Comparative Study (n=60)	Purulo-necrotic tissue rejection, regress of inflammation, natural forming of granulation tissue and accelerated maturing	Bactericidal effect and antibiotic susceptibility of microflora is more marked using ozonomagnetophoresis. Tendency to purulo-necrotic tissue rejection from wound surface, regress of inflammation exudative stage with natural forming of granulation tissue in relatively short terms, its accelerated maturing and reparation are histologicaly marked.	Not reported	Extracted from abstract
4.	MARTÍNEZ-SÁNCHEZ, Gregorio et al. Therapeutic efficacy of ozone in patients with diabetic foot. **European Journal of Pharmacology**, v. 523, n. 1-3, p. 151-161, 2005.	Diabetic foot	Group 1: treated with ozone (local and rectal insufflation of the gas) Group 2: treated with topical and systemic antibiotics 20 days of treatment	Randomized Controlled Clinical Trial (n=101)	Glycemic index, the area and perimeter of the lesions and biochemical markers of oxidative stress and endothelial damage	Ozone treatment improved glycemic control, prevented oxidative stress, normalized levels of organic peroxides, and activated superoxide dismutase. Futhermore, the healing of the lesions improved, resulting in fewer amputations than in control group. These results show that medical ozone treatment could be na alternative therapy in the treatment of diabetes and its complications.	None	The pharmacodynamic effect of ozone in the treatment of patients with neuroinfectious diabetic foot can be ascribed to the possibility of it being a superoxide scavenger. Superoxide is considered a link between the four metabolic routes associated with diabetes pathology and its complications.

Doenças Vasculares Periféricas

Additional Table 3: Peripheral vascular disease indications for O_3 therapy

	Study	Pathology	Concentration and route of O_3 administration	Type of study	Measured parameter(s)	Results	Side effect(s)	Mechanism of action
1.	MAKAROV, I. V.; SHCHUKIN, Y. V.; LUKASHOVA, A. V. Effect of combined application of ozone therapy and gravitational therapy on the remote results of complex treatment of geriatric patients. **Advances in gerontology= Uspekhi gerontologii**, v. 30, n. 4, p. 558-562, 2017.	Obliterating Atherosclerosis of arteries of the lower extremities	Group 1: 1A) Intravenous ozonized physiological solution 1B) ozonized autohemotherapy Group 2: 2A) medical therapy in combination with ozonized physiological solution and gravitational therapy 2B) standard medical therapy in conjunction with major ozonized autohemotherapy and gravitational therapy Group Control: standard medical therapy	Prospective Randomized Study in three parallel groups (n=139)	Survival analysis and probable risk	Analysis of survival and probable risk at 7 years of follow-Cox regression method revealed a maximum efficiency in the subgroup 2a where the risk of probability of surgeries and also increases in a stage of a disease effectively decreased.	Not reported	Extracted from abstract
2.	ZHOU, Yi-Ting et al. Ozone Gas Bath Combined with Endovenous Laser Therapy for Lower Limb Venous Ulcers: A Randomized Clinical Trial. **Journal of Investigative Surgery**, v. 29, n. 5, p. 254-259, 2016.	Lower Limb Venous Ulcers	Receive ozone gas bath combined with EVLT (OEVLT group) or EVLT alone (EVLT group). In the OEVLT group, the venous ulcers were preconditioned with ozone gas bath prior to EVLT. The minimum follow-up time was 12 months.	Randomized Clinical Trial (n=92)	The two groups were compared in terms of complete occlusion of the treated veins, ulcer healing ratio, ratio of ulcer recurrence, patient satisfaction, complications, and side effects	Ozone gas bath combined with EVLT showed improved efficacy for the treatment of lower limb venous ulcers and lower recurrence ratio comparison with EVLT alone. This procedure is a safe and technically feasible.	None	Extracted from abstract
3.	SOLOVASTRU, Laura Gheuca et al. Randomized, controlled study of innovative spray formulation containing	Chronic Venous Leg Ulcers	Application of both ozonated oil and α-bisabolol or the control cream (vitamin A, vitamin E, talc, and zinc oxide) for 30 days	Randomized controlled trial; (n=29)	Patients were evaluated on 4 different visits: at days 0, 7, 14, and 30. At each visit, the wound surfaces were	At the end of treatment, the proportion of patients with complete ulcer healing was higher with ozonated oil and α-bisabolol formulation (25% vs 0%). Furthermore, the changes in ulcer surface area	Not reported	Extracted from abstract

Doenças Vasculares Periféricas

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Additional Table 3: Peripheral vascular disease indications for O_3 therapy

Study	Pathology	Concentration and route of O_3	Type of study	Measured parameter(s)	Results	Side effect(s)	Mechanism of action
ozonated oil and α-bisabolol in the topical treatment of chronic venous leg ulcers. **Advances in skin & wound care**, v. 28, n. 9, p. 406-409, 2015.				measured. Wound area ratio and the speed of ulcer healing were calculated.	were significant for ozonated oil and α-bisabolol formulation only ($P < .05$), in particular, observing a significant and progressive reduction of the wound surface by 34%, 59%, and 73%, after 7, 14, and 30 days of treatment, respectively.		
TYLICKI, L. et al. The influence of ozonated autohemotherapy on oxidative stress in hemodialyzed patients with atherosclerotic ischemia of lower limbs. **The International journal of artificial organs**, v. 26, n. 4, p. 297-303, 2003.	Hemodialyzed Patients with Atherosclerotic Ischemia of Lower Limbs	Ozone autohemotherapy with ozone concentration of 50 µg / ml per gram of blood in 9 sessions	Prospective, Controlled, Single Blind Study (n=12)	The protein and lipid peroxidation products, the reduced glutathione level in red blood cells and free hemoglobin plasma concentration were measured.	A significant decrease in GSH level and a little increment in lipid peroxidation extent, as well as the fact that a lower dose of ozone (i.e. 35 µg/ml) may also provide beneficial clinical effects in HD patients.	None	It seems likely that the antioxidant defense system, part of which is glutathione, neutralizes oxidative properties of ozone in this concentration and protects against oxidative cell damage.

Doenças Neurológicas

Additional Table 4: Neurological indications for O_3 therapy							
Study	Pathology	Concentration and route of O_3 administration	Type of study	Measured parameter(s)	Results	Side effect(s)	Mechanism of action

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Patologias de Cabeça e Pescoço

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Additional Table 5: Head and neck indications for O3 therapy							
Study	Pathology	Concentration and route of O3 administration	Type of study	Measured parameter(s)	Results	Side effect(s)	Mechanism of action
SÖNMEZ, Onur et al. The evaluation of ozone and betahistine in the treatment of tinnitus. **European Archives of Oto-Rhino-Laryngology**, v. 270, n. 7, p. 1999-2006, 2013.	Tinnitus	Ozone group: 10 sessions of ozone treatment via major autohemotherapy Betahistine group: 48 mg/day betahistine tablets per oral for 3 months duration Control group: any treatment	Randomized, Prospective Controlled Study (n=68)	Tinnitus loudness and tinnitus handicap inventory (THI)	Comparison of the initial mean THI and 3 and 6 months after treatment revealed a significant difference in ozone and betahistine groups but not in the control group.	Not reported	Extracted from abstract
RAGAB, A. et al. Randomised, double-blinded, placebo-controlled, clinical trial of ozone therapy as treatment of sudden sensorineural hearing loss. **The Journal of Laryngology & Otology**, v. 123, n. 1, p. 54-60, 2009.	Sudden sensorineural hearing loss	Patients received placebo (15 patients) or ozone therapy (autohemotherapy, 30 patients). For the last treatment, 100 ml of the patient's blood were immediately treated with a gaseous mixture of oxygen and 1: 1 ozone (from an ozone generator) and reinjected into the patient by intravenous infusion. Treatments were administered twice a week for 10 sessions	Prospective, randomised, double-blinded, placebo-controlled, parallel group, clinical trial (n=45)	The following data were recorded: pre- and post-treatment mean hearing gains; air and bone pure tone averages; speech reception thresholds; speech discrimination scores; and subjective recovery rates	Significant recovery was observed in 23 patients (77 per cent) receiving ozone treatment, compared with six (40 per cent) patients receiving placebo ($p < 0.05$). Mean hearing gains, pure tone averages, speech reception thresholds and subjective recovery rates were significantly better in ozone-treated patients compared with placebo-treated patients ($p < 0.05$). Ozone therapy is a significant modality for treatment of sudden sensorineural hearing loss	None	Extracted from abstract
CASTILLO VÁZQUEZ, Carmen et al. Acupuntura y ozonoterapia en pacientes con glaucoma crónico simple. **MEDISAN**, v. 11, n. 2, 2007.	Simple chronic glaucoma	10 daily sessions, obeying the rules of procedure and the forms of application: systemic and rectal	Clinical-therapeutic trial; Two groups; Group I; acetazolamide and mannitol and Group II: acupuncture and ozonotherapy (n = 48)	Time of evolution in years, visual acuity, papillary excavation and intraocular pressure - IOP	The advantages of the present process to achieve normalization and stabilization of IOP figures have been identified, prevention of the progression of optic nerve lesions and possible evolution to blindness without having to resort to surgery	Not reported	Activation of cellular metabolism, microcirculation improvement and ocular hydrodynamics, especially the drainage system; increased delivery of oxygen to these

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Additional Table 5: Head and neck indications for O_3 therapy

Study	Pathology	Concentration and route of O_3 administration	Type of study	Measured parameter(s)	Results	Side effect(s)	Mechanism of action
							tissues as well as nutrients that contribute to their trophism, especially oxygen and the stimulation of enzyme systems protecting against degenerative processes
RODRÍGUEZ ACOSTA, Mireida et al. La ozonoterapia en la neuropatía epidémica forma óptica¿ Beneficio y riesgo? **Rev. Cuba. oftalmol**, v. 7, n. 1/2, p. 39-51, 1994.	Optical form Epidemic Neuropathy	11 treatment schemes: dexamethasone, methylprednisolone, hydroxycobalamin + methionine + sodium thiosulfate, vitamins, magnetotherapy, ozone therapy, hyperbaric oxygenation, endonasal electrophoresis with vitamin B1, transference factor, interferon (INF) natural alpha and recombinant interferon alfa 2b Group control: basic vitamins	Multicentre Therapeutic Clinical Trial (n=576)	Extracted from Abstract	The treatment with ozone showed statistically significant differences ($p < 0.05$) (in each of the evaluation cuts made) in terms of improvement and recovery of cases treated with this procedure. In the rest of the therapeutic schemes employed no significant differences are found.	Not reported	Extracted from abstract

Patologias Ortopédicas

Additional Table 6: Orthopedic indications for O_3 therapy

	Study	Pathology	Concentration and route of O_3 administration	Type of study	Measured parameter(s)	Results	Side effect(s)	Mechanism of action
1.	DUYMUS, Tahir Mutlu et al. Choice of intra-articular injection in treatment of knee osteoarthritis: platelet-rich plasma, hyaluronic acid or ozone options. **Knee Surgery, Sports Traumatology, Arthroscopy**, v. 25, n. 2, p. 485-492, 2017.	Knee Osteoarthritis	Group 1 (PRP): received intra-articular injection of PRP × 2 doses Group 2 (HA) received a single dose of HÁ Group 3 (Ozone) received ozone × 4 doses	Randomized Controlled Clinical Trial (n=102)	WOMAC and VAS scores	In the treatment of mild–moderate knee OA, PRP was more successful than HA and ozone injections, as the application alone was sufficient to provide at least 12 months of pain-free daily living activities.	Not reported	Extracted from abstract
2.	GIOMBINI, A. et al. Comparison between intrarticular injection of hyaluronic acid, oxygen ozone, and the combination of both in the treatment of knee osteoarthrosis. **Journal of biological regulators and homeostatic agents**, v. 30, n. 2, p. 621-625, 2016. (PMID: 27358159)	Osteoarthrosis (OA)	Randomized to intra-articular injections of hyaluronic acid (HÁ), or oxygen ozone (O2O3) or combined one per week for 5 consecutive weeks	Comparative Study, Randomized Controlled Trial (n=70)	KOOS questionnaire and visual analog scale (VAS)	The combination of O2O3 and HA treatment led to a significantly better outcome especially at 2-month follow-up compared to HA and O2O3 given separately to patients affected by OA of the knee.	Not reported	Extracted from abstract
3.	PERRI, Marco et al. Indications and efficacy of O 2–O 3 intradiscal versus steroid intraforaminal injection in different types of disco vertebral pathologies: a prospective randomized double-blind trial with 517 patients. **Radiologia medica**, v. 121, n. 6, p. 463-471, 2016. (6)	Discal pathologies	intraforaminal interlaminar space and intradiscal injection of ozone 8-10mL @28mcg/mL + (4mg/2mL bethametasone) perigangliar (n=257) x 4mg/2mL bethametasone perigangliar	Prospective randomized double-blind trial (n=517)	Visual Analog Scale Questionnaire for 6-month	After 6 months, O2–O3 discolysis was successful in 106 (41.24 %) Study Group patients with extrusions compared with 9 Control Group patients (3.5 %) ($P < 0.001$). In 89 (34.6 %) Study Group patients with protrusions, success rate was statistically significant compared with 5 Control Group patients (1.9 %). Significant difference	Not reported	Intradiscal O2–O3 mixture injection produces a dehydration and chemiodiscolysis of nucleus pulposus proteo- glycans, because ozone causes an oxide reduction process called ozonolysis; reacts with organic molecules containing double or triple bonds, leading to disc

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Additional Table 6: Orthopedic indications for O3 therapy

Study	Pathology	Concentration and route of O3 administration	Type of study	Measured parameter(s)	Results	Side effect(s)	Mechanism of action
					was detected in the presence of Grade I, II, III of Degenerated Disc in 185 of Study Group patients (68.4 %) compared with 4 Control Group patients (1.5 %)		shrinkage and reduction of compression of the nerve roots. Has analgesic and antiinflammatory properties to disc herniations. acts on radiculitis, an action that is achieved with injection of the mixture in the periangliar site.Differences in success rate between study and control groups became significant only after 6 months, the efficacy of steroids and anesthetic drugs administered to both groups is temporary.
PERRI, Marco et al. T2 shine-through phenomena in diffusion-weighted MR imaging of lumbar discs after oxygen–ozone discolysis: a randomized, double-blind trial with steroid and O2–O3 discolysis versus steroid only. **Radiologia medica**, v. 120, n. 10, p. 941-950, 2015. (5)	Lumbar disc herniation	control group (n=77) intraforaminal and epidural injection of 4mg/2mL of bethametasone and anaesthetic (2-3mL ropivacaine 2%) x study group (n=77) : same protocol of CG+ 6mL intradiscal + 4mL intraforaminal @ 28mcg/mL	Randomized - double-blind trial (n=154)	An intervertebral disc volumetric analysis (IDVA), DWI signal score and post treatment clinical outcome evaluation were performed for an assessment of hernia reduction	In the Study Group, 58 over 77 patients had a successful outcome (Responders). In the Responders group, DWI T2 shine-through effect was present during MRI follow-up and in particular in 53 of 77 patients in the 6 months of follow-up ($P < 0.05$). Discs' shrinkage in the sixth month of follow-up ($P < 0.05$) as showed by IDVA. T2 shine-through effect in DWI is present before morphological disc reduction and moreover could be considered as a	Not reported	Statistically significant increment of T2 shine- through effect, in the study group from the second MRI follow-up after percutaneous treatments with ozonolysis. These discal signal changes are not detectable with MRI standard protocols. Therefore, we could say that in the treated discs, the presence of T2 shine-through effect

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Additional Table 6: Orthopedic indications for O_3 therapy

Study	Pathology	Concentration and route of O_3 administration	Type of study	Measured parameter(s)	Results	Side effect(s)	Mechanism of action
					predictive sign of response to oxygen–ozone treatment		
ZHANG, Yafeng et al. Treatment of the lumbar disc herniation with intradiscal and intraforaminal injection of oxygen-ozone. **Journal of back and musculoskeletal rehabilitation**, v. 26, n. 3, p. 317-322, 2013. DOI 10.3233/BMR-130386 (2)	Low back pain and radicular pain due to lumbar disc herniation	Intradiscal and intraforaminal injection of: Group A: oxygen-ozone 10mL @ 25-30mcg/mL (n=90) and Group B: same tratament with additional injection of betamethasone 2mg/1mL (n=82)	Prospective study, randomly – Level of Evidence: 1-1, separated 2 groups (n=172)	Pain relief – at 3 weeks, 6 and 12-month VAS & Japanese Orthopedic Association Score (JOA Score)	Without differences at end of study. At 3 weeks JOAS Score better at ozone isolated. Oxygen-ozone nucleolysis provides excellent pain relief in most herniated disc patients who failed to respond to conservative therapy (1)AM	Not reported	Intradiscal = Inhibition of the production of inflammatory substances and pain mediators (prostaglandins, bradykinins). Increased pro-inflammatory antagonists. Intra-foraminal - Reduction of herniated disc pressure on the root.
ZHANG, Y. C. et al. Lumbar disc herniation treated with Shu-needle therapy and ozone injection of low concentration. **Zhongguo zhen jiu= Chinese acupuncture & moxibustion**, v. 32, n. 9, p. 829-832, 2012.	Lumbar Disc Herniation	Shu-needle therapy group: combination with ozone injection of low concentration. Acupotomy group: conventional acupotomy therapy plus combination with ozone injection of low concentration. once every 10 days, 3 treatments made one session	Randomized Controlled Trial (n=130)	Clinical efficacy: scores of visual analogue scale (VAS) and Oswestry disability index (ODI)	The clinical curative rate was 69.2% (45/65) and the total effective rate was 96.9% (63/65) in the Shu-needle therapy group. The curative rate was 43.1% (28/65) and the total effective rate was 84.6% (55/65) in the acupotomy group. In comparison, the efficacy of the Shu-needle therapy group was superior to that of the acupotomy group ($P < 0.01$, $P < 0.05$).	**No reported**	**Extracted from abstract**
GAUTAM, Sujeet et al. Comparative Evaluation of Oxygen-Ozone Therapy and Combined Use of Oxygen-Ozone Therapy with Percutaneous Intradiscal Radiofrequency Thermocoagulation for the Treatment of Lumbar	Lumbar Disc Herniation	Ozone group received intradiscal oxygen-ozone therapy (4 to 7 mL of oxygen ozone mixture); ozone-PIRFT group received a combination of oxygen-ozone therapy with PIRFT (radiofrequency	Randomized Controlled Trial (n=91)	Clinical efficacy: visual analog scale (VAS) for pain and the Oswestry disability index (ODI)	VAS scores and ODI were significantly decreased by both ozone and ozone-PIRFT when compared with the baseline values at all points of follow-up. Ozone-PIRFT also resulted in a significant change in all secondary	**No reported**	**Extracted from abstract**

Patologias Ortopédicas

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Additional Table 6: Orthopedic indications for O3 therapy

Study	Pathology	Concentration and route of O3 administration	Type of study	Measured parameter(s)	Results	Side effect(s)	Mechanism of action
Disc Herniation. **Pain Practice**, v. 11, n. 2, p. 160-166, 2011.		lesioning at 80°C for 360 s). Periodic analysis for 1 year			measures at all points of follow-up, as compared with the ozone group		
MELCHIONDA, D. et al. Treatment of radiculopathies: a study of efficacy and tollerability of paravertebral oxygen-ozone injections compared with pharmacological anti-inflammatory treatment. **Journal of biological regulators and homeostatic agents**, v. 26, n. 3, p. 467-474, 2012. PMID: 23034266 (1)	Lumbar radiculopathies due to disc herniations L4-L5 and L5-S1	A) 20 patients treated with lumbar paravertebral injections of Oxygen and ozone; X B) 18 patients treated pharmacologically with antinflammatory-analgesic drugs.	Prospective study, randomly – separated 2 groups A and B (n=38)	Visual Analogue Scale and Oswestry Disability Index. All patients underwent a clinical and neurological examination at baseline (T1) and after 1 (T2), 2 (T3), 4 weeks (T4) and after 3 (T5) and 6 months (T6). An MRI and EMG examination were performed at baseline and after 6 months.	We found a reduction of pain and discomfort soon after one week with oxygen-ozone injections compared with pharmacological treatment, but this difference of response became statistically significant after two weeks (50 percent vs 16.6 percent) and is confirmed after 3 and 6 months, when 80 percent of patients treated with injections turned out pain free compared with half of the patients treated pharmacologically. The paravertebral injections of oxygen-ozone represent a rapidly effective therapy, easily practicable and secure, in patients with lumbar radicolopathies secondary to disc herniation	None	That oxygen-ozone injections in paravertebral regions can induce a direct reduction of root inflammation with a corresponding reduction of pain
PAOLONI, Marco et al. Intramuscular oxygen-ozone therapy in the treatment of acute back pain with lumbar disc herniation: a multicenter, randomized, double-blind, clinical trial of active and simulated lumbar paravertebral injection. Spine, v. 34, n. 13, p. 1337-1344, 2009. (3)	Acute Low Back Pain (LBP) with Lumbar Disc Herniation (HDL)	15 injections (3/week x 5 weeks) intramuscular paravertebral 20mL 20mcg/Ml (n=36) versus sham injection (n=24)	Multicenter, Randomized, Double-Blind, Clinical Trial (n=60)	Patients were observed up to assess pain intensity, LBP-related disability, and drug intake	Patients who received O2O3 had a lower mean pain score than patients who received simulated therapy throughout the observation period. A significant improvement was observed in LBP-related disability in the study group patients when compared with the control group patients. Active O2O3 therapy	None	(i) the inhibited synthesis of proinflammatory prostaglandins, the release of bradykinin, or the release of algogenic compounds; (ii) the increased release of antagonists or soluble receptors that neutralize proinflam- matory

Patologias Ortopédicas

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Additional Table 6: Orthopedic indications for O_3 therapy

Study	Pathology	Concentration and route of O_3 administration	Type of study	Measured parameter(s)	Results	Side effect(s)	Mechanism of action
					was followed by a significantly lower number of days on nonsteroidal anti-inflammatory drugs at V2 and V3 and by a lower number of days at V4		cytokines, such as interleukin (IL)-1, IL-2, IL-8, IL-12, IL-15, interferon, and tumor necrosis factor (TNF); (iii) the increased release of immunosuppressor cytokines, such as transforming growth factor-1 and IL-10
ANSEDE ALONSO, J. C.; CONTRERAS JOYA, M.; PÉREZ HIDALGO, S. Estudio prospectivo y aleatorizado em pacientes com lombalgias o lumbociatálgias tratados com ozonoterapia. **Patología del aparato locomotor**, v. 5, n. 1, p. 46-54, 2007	Low back pain and patients affected of sciatic pain	Group A (lumbago): paravertebral infiltrations of ozone => concentration 23µgrs / ml, injecting 20 cc in each point to infiltrate + analgesia with paracetamol 500mgrs / 8 hrs. Group B (lumbotic and sciatic) treated with intradiscal (ID) and paravertebral ozone (3 or 5 sessions) : concentration 30µgrs / ml, in the amount of 7 to 10 cc in each level + paracetamol 500mgrs / 8hrs as analgesias. Control group: rest + paracetamol 500mgrs / 6 hrs. Monitoring Clinical was 6 months	Prospective and randomized study, controlled trial (n=103)	They were evaluated with the pain intensity scale, Oswestry questionnaire, hand-ground distance, Lasseguè and labor incorporation.	Scale for the intensity of pain and the Oswestry questionnaire for all the patients with low back pain (ozone or conservative treatment) was found an improvement of their symptoms (p0.001). For the group of sciatic pain treated with ozone we found improvement of the pain after the treatment (p0,001) and the Oswestry questionnaire 40,4% (p0.001).The Lasseguè test was negative or improved in 83,2% patients after the treatment in the ozone group.	In the technique of paravertebral infiltration (752 infiltrations on 75 patients) were presented 5 headaches, all disappeared between 24 and 48 hours. 2 patients presented persistent pain at the point of entry. . Underwent infiltrations intradiscal (72 total infiltrations in 48 patientes), 7 presented headaches	No reported

Patologias Ortopédicas

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Additional Table 6: Orthopedic indications for O_3 therapy

Study	Pathology	Concentration and route of O_3 administration	Type of study	Measured parameter(s)	Results	Side effect(s)	Mechanism of action
						for 1 or 2 days although one patient presented persistent headache that lasted 7 days and it was resolved with vasodilator.	

Patologias Ortopédicas

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Additional Table 6: Orthopedic indications for O3 therapy

Study	Pathology	Concentration and route of O3 administration	Type of study	Measured parameter(s)	Results	Side effect(s)	Mechanism of action
DUYMUS, Tahir Mutlu et							
GALUCCI, Massimo et al. Sciatica: Treatment with Intradiscal and Intraforaminal Injections of Steroid and Oxygen-Ozone versus Steroid Only. **Radiology**: Volume 242: Number 3—March 2007 (8)	Radicular pain related to acute lumbar disk herniation	intraforaminal + intradiscal A = Triamcinolone 80mg/2mL) + Ropivacaine 2% 4mL (n=77) B= same of A + O2-O3 5-7mL 28mcg/mL (n=82)	Randomized Clinical Trial (n= 159)	After 6 months, treatment was successful in 36 (47%) patients in group A and in 61 (74%) patients in group B. The difference was significant (P .01)	Intraforaminal and intradiscal injections of a steroid, an anesthetic, and O2-O3 are more effective at 6 months than injections of only a steroid and an anesthetic in the same sites	None	Chemodiscolysis, with ozonolysis of nucleus pulposus proteoglycans, loss of water, and dehydration. Progressive degeneration with fibrous replacement occurs followed, finally, by disk shrinkage; loss of disk volume and direct reduction of root compression. Dehydration of the fibrillary matrix of the nucleus pulposus, vacuole formation, and collagen fragmentation. The reduction of herniated disk volume decreases root edema and venous stasis, stopping the demyelination process. Analgesic and antiinflammatory effects. Iinhibits the synthesis and release of prostaglandins, bradykinin, and various algogenic molecules.

Patologias Ortopédicas

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Additional Table 6: Orthopedic indications for O3 therapy

Study	Pathology	Concentration and route of O3 administration	Type of study	Measured parameter(s)	Results	Side effect(s)	Mechanism of action
							Increases the release of antagonists of proinflammatory cytokines. Solve or decrease chemical radiculitis. Clinical effectiveness of intraforaminal O2-O3 injection without intradiscal therapy
WEI, C. J. et al. Percutaneous intradiscal oxygen-ozone injection for lumbar disc herniation: no need of perioperative antibiotic prophylaxis. **Nan fang yi ke da xue xue bao= Journal of Southern Medical University**, v. 27, n. 3, p. 384-386, 2007.	Lumbar disc herniation	Patients in prophylaxis group:cephalothin V(2.0 g) intravenous 30 min before the operation Control group did not use any antibiotics. *All the patients were injected with 6-10 ml ozone (40 microg/ml) into the discs with followed by 10 ml ozone into the paravertebral space .	Randomized controlled trial (n=72)	Infection evidence : Body temperature as well as results of three routine tests (blood, urine, stool) and C-reactive protein (CRP) level	No infection was found in these patients, nor were any significant differences noted in the results of the examinations between the two groups after controlling in patients with above-normal white blood cell count, neutrophil percentage and CRP level	No reported	Extracted from abstract
ZHANG, Yan; CHEN, Feng; WU, Song. Clinical observation on O3 acupoint injection for treatment of low back pain. **Zhongguo zhen jiu= Chinese acupuncture & moxibustion**, v. 27, n. 2, p. 115-116, 2007.	Low back pain	Electroacupuncture (EA) group: a Danggui injectio point injection group and an O3 acupoint injection group. They were treated with EA, Danggui acupoint injection and O3 (30 microg/mL) acupoint injection at Qihaishu (BL 24), Dachangshu (BL 25), Guanyuanshu (BL 25) and local Ashi points.	Randomized Controlled Trial (n=120)	Clinical parameters of pain	There were significant differences in the therapeutic effect as the O3 acupoint injection group compared with the EA group and the Danggui point injection group ($P < 0.01$ or $P < 0.05$), but there was no significant difference between the EA group and the Danggui point injection group ($P > 0.05$).	No reported	Extracted from abstract

Doenças Gastro-intestinais

Additional Table 7: Gastrointestinal indications for O_3 therapy							
Study	Pathology	Concentration and route of O_3 administration	Type of study	Measured parameter(s)	Results	Side effect(s)	Mechanism of action
1. GENG, Yan et al. Ozone therapy combined with sulfasalazine delivered via a colon therapy system for treatment of ulcerative colitis. **Nan fang yi ke da xue xue bao= Journal of Southern Medical University**, v. 30, n. 12, p. 2683-2685, 2010.	Ulcerative Colitis	3 groups - Each group was given sulfasalazine at the daily dose of 2 g, and in colon therapy group and ozone therapy plus sulfasalazine therapy group, sulfasalazine was delivered via a colon therapy system on a daily basis; the control group received sulfasalazine via retention enema only	Randomized Controlled Trial (n=54)	At 0, 2, and 4 weeks of the treatment, colonoscopy was performed to evaluate the disease activity, and biopsy samples were obtained at 0 and 4 weeks for histological examination.	In comparison with colon therapy group and control group, ozone therapy plus colon therapy resulted in more rapid alleviation of the clinical symptoms and better histological improvement. Ozone therapy combined with sulfasalazine delivered via a colon therapy system is feasible and effective for treatment of ulcerative colitis	None	Extracted from abstract
2. JIAO, X. J.; PENG, Xun. Clinilal study of medical ozone therapy in chronic hepatitis B of 20 patients. **Zhonghua shi yan he lin chuang bing du xue za zhi= Zhonghua shiyan he linchuang bingduxue zazhi= Chinese journal of experimental and clinical virology**, v. 22, n. 6, p. 484-485, 2008. (PMID: 19544653)	Chronic Hepatitis B	Group control: basic therapy Treatment group: basic therapy plus ozone therapy 8 weeks	Comparative Study, Randomized Controlled Trial (n=42)	Index of biochemistry and virology	After the treatment, liver function of the treatment group and the control group had more significant improvement. The treatment group complete effective and partial effective were 10% and 35% difference. The control group complete effective and partial effective were 4.6% and 13.6% ($P < 0.05$). Treatment of medical ozone on patients with chronic hepatitis B is effective.	Not reported	Extracted from abstract

Patologias Genito-urinárias

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Additional Table 8: Genitourinary indications for O_3 therapy

Study	Pathology	Concentration and route of O_3 administration	Type of study	Measured parameter(s)	Results	Side effect(s)	Mechanism of action
GU, Xi-bing et al. Effect of medical ozone therapy on renal blood flow and renal function of patients with chronic severe hepatitis. **Chinese medical journal**, v. 123, n. 18, p. 2510-2513, 2010. (PMID: 21034619)	Chronic Severe Hepatitis	ozone therapy group: basic treatments plus ozone therapy system (basic autohemotherapy) - One hundred milliliter venous blood was drawn from each patient, and was mixed with 100 ml (35 μg/ml) medical ozone and then was returned the blood to the patient intravenously, once every other day for 20 days. control group: basic treatments	Randomized Controlled Trial (n=85)	PRA, AII, ALD, renal blood flow, damage to renal function and Survival rates	Ozone therapy group, PRA was (1.31 ± 0.12) $ng \cdot ml^{-1} \cdot h^{-1}$, AII (111.25 ± 17.35) pg/ml, ALD (251.31 ± 22.60) pg/ml, which decreased significantly compared with those before treatment (PRA (2.23 ± 0.13) $ng \cdot ml^{-1} \cdot h^{-1}$, AII (155.18 ± 19.13) pg/ml, ALD (405.31 ± 29.88) pg/ml, t = 4.67 - 14.23, P < 0.01), also lower than those of control group 20 days after the treatment (PRA (2.02 ± 0.11) $ng \cdot ml^{-1} \cdot h^{-1}$, AII (162.21 ± 15.32) pg/ml, ALD (401.20 ± 35.02) pg/ml, t = 4.97 - 15.61, P < 0.01); renal blood flow was (175.15 ± 28.20) ml/min, which increased compared with that before the treatment ((125.68 ± 21.25) ml/min) and was higher than that of control group 20 days after the treatment ((128.59 ± 23.15) ml/min, t = 4.78, 4.61, P < 0.01). Renal damage occurred in 2 cases (5%) in ozone therapy group, less than that in control group (9 cases, 21%). 33 cases (77%) in ozone therapy group vs. 16 cases (38%) in control group survived.	Not reported	Extracted from abstract

Doenças Respiratórias

1.

Additional Table 9: Respiratory indications for O_3 therapy							
Study	Pathology	Concentration and route of O_3 administration	Type of study	Measured parameter(s)	Results	Side effect(s)	Mechanism of action
CALUNGA, J. L. et al. Rectal ozone therapy for patients with pulmonary emphysema. **Revista medica de Chile**, v. 139, n. 4, p. 439-447, 2011.	Pulmonary Emphysema	Rectal ozone in 20 daily sessions, rectal medicinal oxygen and repeated three months later in the first two groups	Randomized Controlled Trial (n=64)	At baseline and at the end of the study, spirometry and a clinical assessment were performed.	At baseline, patients on ozone therapy had significantly lower values of forced expiratory volume in the first second (fEV1) and fEV1/forced vital capacity. At the end of the treatment period, these parameters were similar in the three treatment groups, therefore they only improved significantly in the group on ozone therapy. Rectal ozone therapy may be useful in patients with pulmonary emphysema	Not reported	Extracted from abstract

Parâmetros Imunológicos

1.

Additional Table 10: Imunology indications for O_3 therapy							
Study	Pathology	Concentration and route of O_3 administration	Type of study	Measured parameter(s)	Results	Side effect(s)	Mechanism of action
TYLICKI, Leszek et al. No effects of ozonated autohemotherapy on inflammation response in hemodialyzed patients. **Mediators of inflammation**, v. 13, n. 5-6, p. 377-380, 2004.	Peripheral Arterial Disease	9 sessions - ozonated autohemotherapy with an ozone concentration of 50 µg/ml	Controlled, Single-Blind, Cross-Over Study (n=12)	Plasma concentration of C-reactive protein and interleukin-6, markers of inflammation	Autohemotherapy using an ozone concentration of 50 µg/ml does not induce an inflammatory response	Not reported	Extracted from abstract

Parâmetros Metabólicos

1.

Additional Table 11: Metabolic indications for O3 therapy							
Study	Pathology	Concentration and route of O3 administration	Type of study	Measured parameter(s)	Results	Side effect(s)	Mechanism of action
TYLICKI, Leszek et al. Ozonated autohemotherapy in patients on maintenance hemodialysis: influence on lipid profile and endothelium. **Artificial organs**, v. 28, n. 2, p. 234-237, 2004.	Hemodialysis with AIL	Autohemotherapy with oxygen as a control followed by O3-AHT with ozone concentration of 50µg/ml	Prospective, Placebo-Controlled (n=12)	Serum lipids and plasma activity of von Willebrand factor (FvW)	After O3-AHT, total cholesterol significantly decreased compared to the baseline (−8.34%) [*P* < 0.01]. LDL cholesterol was also significantly lower than the initial value (−17.71%) [*P* < 0.001]. No significant changes in the activity of vWF were found after the first session of O3-AHT and after all nine sessions of O3-AHT. The study demonstrated that O3-AHT did not affect deleteriously the endothelium in patients with chronic renal failure on maintenance hemodialysis. It may stimulate beneficial changes in serum lipid profile manifesting as a decrease in the total- and LDL-cholesterol levels.	Not reported	Extracted from abstract

Clinical Trials

Clinical Trials

Clinical Trials							
Study	Pathology	Concentration and route of O_3 administration	Type of study	Measured parameter(s)	Results	Side effect(s)	Mechanism of action
1. DE JESUS, Carlos César Lopes et al. Comparison between intra-articular ozone and placebo in the treatment of knee osteoarthritis: A randomized, double-blinded, placebo-controlled study. **PloS one**, v. 12, n. 7, p. e0179185, 2017.	Symptomatic Knee Osteoarthritis (OA)	Two groups receiving intra-articular 20 µg/ml of ozone (OZ) or placebo (PBO) for 8 weeks	Randomized, Double-blinded, Placebo Controlled Clinical Trial (n=98)	Visual Analogue Scale (VAS), Lequesne Index, Timed Up and Go Test (TUG Test), SF-36, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and Geriatric Pain Measure (GPM)	After 8 weeks of treatment, ozone was more effective than the placebo: VAS [mean difference (MD) = 2.16, p < 0.003 (CI 95% 0.42–3.89)], GPM [MD = 18.94, p < 0.004 (CI 95% 3.43–34.44)], LEQ [MD = 4.05, p < 0.001 (CI 95% 1.10–7.00)], WOMAC (P) [median of diff = 9.999, p = 0.019 (CI 95% 0.000–15.000)], WOMAC (JS) [median of diff = 12.499, p < 0.001 (CI 95% 0.000–12.500)], WOMAC (PF) = [median of diff = 11.760, p = 0.003 (CI 95% 4.409–19.119)], TUG (no statistical difference) and SF-36 (FC) [(MD = -25.82, p < 0.001 (CI 95% 33.65–17.99)], SF-36 (PH) [MD = -40.82, p < 0.001 (CI 95% -54.48–27.17)], SF-36 (GSH) [MD = -3.38, p < 0.001 (CI 95% -4.83–1.93)], SF-36 (SA) [MD = 2.17, p < 0.001 (CI 95% -19.67–8.24), SF-36 (EA) [MD = -35.37, p < 0.001 (CI 95% -48.86–21.89)]	Adverse events occurred in 3 patients (2 in the placebo group and 1 in the ozone group) and included only puncture accidents	Extracted from abstract
2. AYKUT-YETKINER, A. et al. Color assessment after bleaching with hydrogen peroxide versus ozone: a randomized controlled clinical trial. **General dentistry**, v. 65, n. 4, p. e12-e17, 2017.	Color Change of Teeth Bleached	40% hydrogen peroxide (HP) or ozone (OZ)	Randomized controlled clinical trial (n=26)	Maxillary dental arch vacuum trays were constructed with circumferential openings in the middle portion of the maxillary incisors at their labial surfaces. These trays were used for measuring color-first at baseline and then immediately and 48 hours after postbleaching-and were not used in bleaching.	Analysis of the data revealed that, while overall color change (ΔE*) values of the HP and OZ groups did not show statistically significant differences immediately after bleaching (P = 0.114), ΔE* values were significantly different 48 hours postbleaching (P = 0.00). Visible color changes were not obtained with either HP or OZ immediately postbleaching. The greatest visible color change occurred with HP 48 hours postbleaching.	Not reported	Extracted from abstract

PLOS ONE

RESEARCH ARTICLE

Comparison between intra-articular ozone and placebo in the treatment of knee osteoarthritis: A randomized, double-blinded, placebo-controlled study

Carlos César Lopes de Jesus[1]*, Fânia Cristina dos Santos[2], Luciana Maria Oliveira Bueno de Jesus[3], Iara Monteiro[2], Maria Sonia Sousa Castro Sant'Ana[2], Virginia Fernandes Moça Trevisani[1]

1 Department of Evidence-Based Medicine, Paulista School of Medicine, Sao Paulo Federal University, Sao Paulo, Sao Paulo, Brazil, **2** Department of Geriatrics and Gerontology, Paulista School of Medicine, Sao Paulo Federal University, Sao Paulo, Sao Paulo, Brazil, **3** "Dante Pazzanese" Institute of Cardiology, Sao Paulo, Sao Paulo, Brazil

* caceloje@gmail.com

OPEN ACCESS

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Competing interests: The authors have declared that no competing interests exist.

Abstract

Objective

The aim of the trial was to determine the effectiveness of oxygen-ozone injections on knee osteoarthritis concerning pain reduction, joint functional improvement, and quality of life.

Methods

In this randomized, double-blinded, placebo controlled clinical trial, 98 patients with symptomatic knee osteoarthritis (OA) were randomized into two groups receiving intra-articular 20 μg/ml of ozone (OZ) or placebo (PBO) for 8 weeks. The efficacy outcomes for knee OA were the Visual Analogue Scale (VAS), Lequesne Index, Timed Up and Go Test (TUG Test), SF-36, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and Geriatric Pain Measure (GPM).

Results

After 8 weeks of treatment, ozone was more effective than the placebo: VAS [mean difference (MD) = 2.16, $p < 0.003$ (CI 95% 0.42–3.89)], GPM [MD = 18.94, $p < 0.004$ (CI 95% 3.43–34.44)], LEQ [MD = 4.05, $p < 0.001$ (CI 95% 1.10–7.00)], WOMAC (P) [median of diff = 9.999, $p = 0.019$ (CI 95% 0.000–15.000)], WOMAC (JS) [median of diff = 12.499, $p < 0.001$ (CI 95% 0.000–12.500)], WOMAC (PF) = [median of diff = 11.760, $p = 0.003$ (CI 95% 4.409–19.119)], TUG (no statistical difference) and SF-36 (FC) [(MD = -25.82, $p < 0.001$ (CI 95% 33.65–17.99)], SF-36 (PH) [MD = -40.82, $p < 0.001$ (CI 95% -54.48–27.17)], SF-36 (GSH) [MD = -3.38, $p < 0.001$ (CI 95% -4.83–1.93)], SF-36 (SA) [MD = 2.17, $p < 0.001$ (CI 95% -19.67–8.24), SF-36 (EA) [MD = -35.37, $p < 0.001$ (CI 95% -48.86–21.89)]. Adverse events occurred in 3 patients (2 in the placebo group and 1 in the ozone group) and included only puncture accidents.

PLOS ONE

RESEARCH ARTICLE

Comparison between intra-articular ozone and placebo in the treatment of knee osteoarthritis: A randomized, double-blinded, placebo-controlled study

Carlos César Lopes de Jesus[1]*, Fânia Cristina dos Santos[2], Luciana Maria Oliveira Bueno de Jesus[3], Iara Monteiro[2], Maria Sonia Sousa Castro Sant'Ana[2], Virginia Fernandes Moça Trevisani[1]

1 Department of Evidence-Based Medicine, Paulista School of Medicine, Sao Paulo Federal University, Sao Paulo, Sao Paulo, Brazil, 2 Department of Geriatrics and Gerontology, Paulista School of Medicine, Sao Paulo Federal University, Sao Paulo, Sao Paulo, Brazil, 3 "Dante Pazzanese" Institute of Cardiology, Sao Paulo, Sao Paulo, Brazil

* caceloje@gmail.com

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Clinical Trials

3.	LI, Juan-Hong et al. Treatment of middle-aged and aged patients with knee osteoarthritis of yang-deficiency induced cold-damp syndrome by ozone combined Chinese materia medica: a clinical research. **Zhongguo Zhong xi yi jie he za zhi Zhongguo Zhongxiyi jiehe zazhi= Chinese journal of integrated traditional and Western medicine**, v. 33, n. 4, p. 471-475, 2013.	Knee osteoarthritis (KOA) of yang-deficiency induced cold-damp syndrome (YDICDS)	Group C received ozone injection (10 -18 mL) from knee joint cavity at 25 mg/L, once weekly for 4 weeks in total; Group D received injection from knee joint cavity and took FGG	Prospective study-Randomized controlled-clinical trial (n=200)	The efficacy was assessed using visual analogue scale (VAS) and Western Ontario MacMaster University Osteoarthritis index (WOMAC)	The cured and markedly effective rate was 76.0% in Group D, higher than that of Group A (25. 0%), Group B (25. 0%), and Group C (43.8%), respectively ($P < 0.05$). Ozone combined FGG had advantages in alleviating joint pain and improving joint stiffness and daily activities of middle-aged and aged patients with KOA of YDICDS.	Not reported	Extracted from abstract
4.	MARTÍNEZ-SÁNCHEZ, Gregorio et al. Effects of ozone therapy on haemostatic and oxidative stress index in coronary artery disease. **European journal of pharmacology**, v. 691, n. 1-3, p. 156-162, 2012.	Coronary artery disease (CAD)	Group 1: treated with antithrombotic therapy and other Group 2: treated with antithrombotic therapy plus rectal insufflation of O3 Parallel group: age and gender matched was used as reference for the experimental variables	Randomized Parallel Controlled Clinical Trial (n=53)	Comparing hemostatic indexes and biochemical markers of oxidative	Ozone treatment significantly ($P<0.001$) improved prothrombin time when compared to the antithrombotic therapy only group, without modifying bleeding time. Combination antithrombotic therapy +O3 improved the antioxidant status of patients reducing biomarkers of protein and lipid oxidation, enhancing total antioxidant status and modulating the level of superoxide dismutase and catalase with a 57% and 32% reduction in superoxide dismutase and catalase activities respectively, moving the redox environment to a status of low production of O2 with an increase in H2O2 detoxification.	None	Extracted from abstract

Clinical Trials

5.

DI PAOLO, Nicola et al. Extracorporeal blood oxygenation and ozonation (EBOO): a controlled trial in patients with peripheral artery disease. 2005	Peripheral Artery Disease (PAD)	Group 1: treated with antithrombotic therapy Group 2: treated with antithrombotic therapy plus rectal insufflation of O3 Parallel group: age and gender matched was used as reference for the experimental variables.	Randomized Double Controlled Trial (n=28)	Skin lesions and pain, and improvement in quality of life and vascularisation	Patients treated with EBOO showed highly significant regression of skin lesions with respect to patients treated with prostacyclin. Other parameters that were significantly different in the two groups of patients were pain, pruritus, heavy legs and well-being. No significant differences in vascularisation of the lower limbs before and after treatment were found in either group.	None	Extracted from abstract

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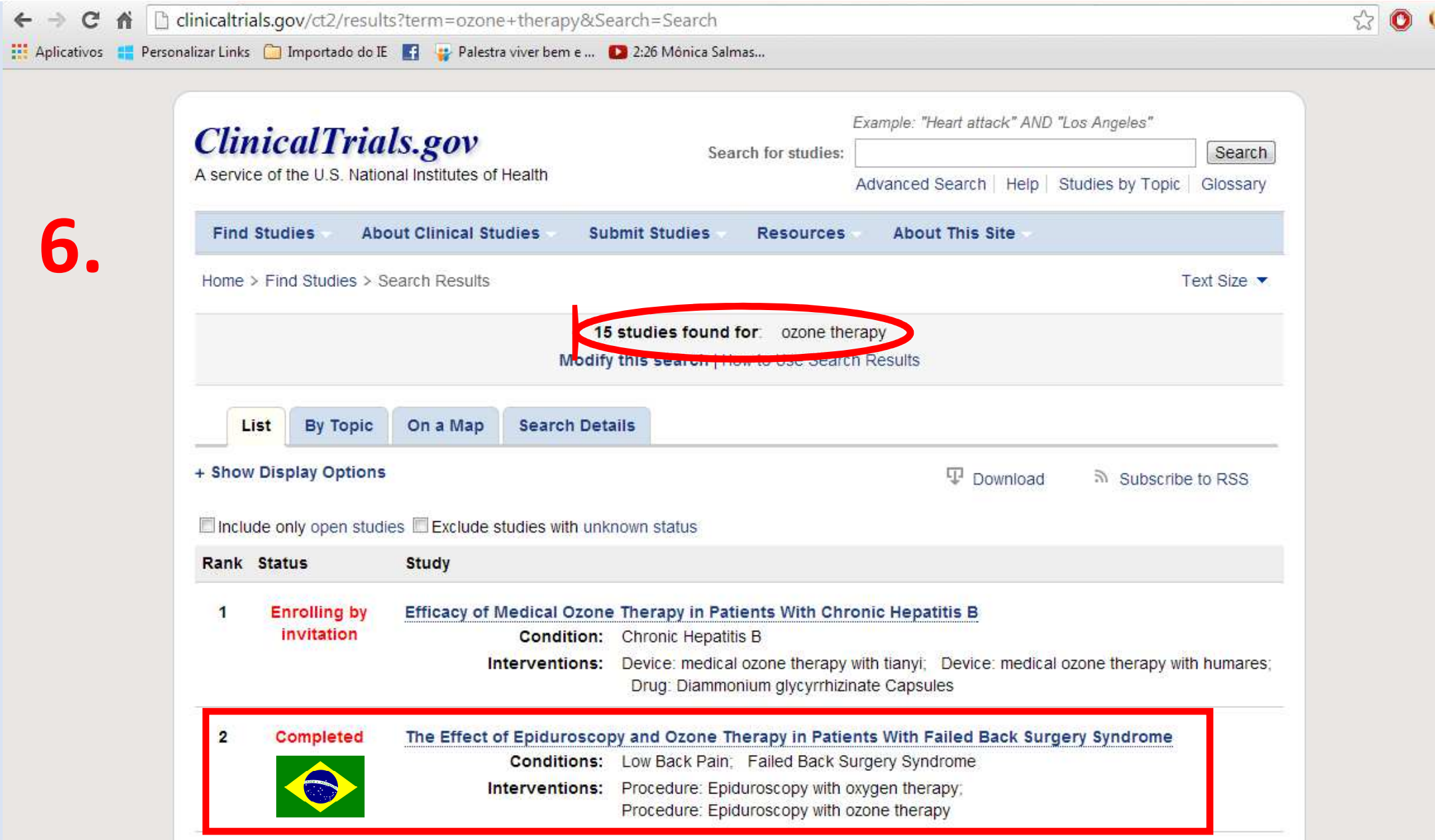
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Efficacy of Medical Ozone Therapy in Patients With Chronic Hepatitis B
Condition: Chronic Hepatitis B
Interventions: Device: medical ozone therapy with tianyi; Device: medical ozone therapy with humares; Drug: Diammonium glycyrrhizinate Capsules
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The Effect of Epiduroscopy and Ozone Therapy in Patients With Failed Back Surgery Syndrome
Conditions: Low Back Pain; Failed Back Surgery Syndrome
Interventions: Procedure: Epiduroscopy with oxygen therapy; Procedure: Epiduroscopy with ozone therapy

Tese apresentada à Faculdade de Medicina da Universidade de São Paulo para obtenção do Título de Doutor em Ciências
Programa de Pós-graduação do Departamento de Neurologia

Epiduroscopia e Ozonioterapia no Tratamento da Síndrome Dolorosa Pós-laminectomia: estudo comparativo, aleatorizado, duplamente encoberto e controlado por placebo

Aluno: Francisco Nêuton de Oliveira Magalhães

Orientador: Prof. Dr. Erich Talamoni Fonoff

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ORIGINAL RESEARCH

Effects of ozone applied by spinal endoscopy in patients with chronic pain related to failed back surgery syndrome: a pilot study

Francisco Nêuton de Oliveira Magalhães
Sandra Correia Soares
Jaqueline Melo Torres
Arthur Ungaretti
Mariana Fillipi Cacciacarro
Manoel Jacobsen Teixeira
Erich Talamoni Fonoff

Pain Center and Division of Functional Neurosurgery, Department of Neurology, School of Medicine, University of São Paulo, São Paulo, Brazil

Introduction: In the last two decades, ozone has emerged as a treatment for low back pain, applied by means of minimally invasive techniques.

Objective: The aim of this study is to assess the effect and safety of ozone therapy applied in the epidural space for chronic pain related to failed back surgery syndrome.

Methods: The investigators studied 13 sequential patients of both sexes, between 18 and 70 years old, with persistent chronic pain (more than six months) in the lumbar region and in the lower limbs related to failed back surgery syndrome (FBSS). Pain was classified as neuropathic and non-neuropathic regarding the topography (lumbar and lower limb), based on the DN4 (Douleur Neuropathique 4) questionnaire. The patients received the ozone gas in the lumbar epidural space via spinal-sacral endoscopy. Clinical evaluation was performed before, immediately after (24 hours), and 1, 3, and 6 months after intervention with visual analog scale and Oswestry Disability Index (ODI).

Results: Overall, the patients had 43.7% reduction of lumbar pain, 60.9% reduction in leg pain in six months followed by 44.0% of improvement in ODI. The reduction of pain and in the disability index was markedly greater in patients with non-neuropathic predominant pain, 95.2%, 80.6%, and 75.3% improvement in lumbar, leg pain, and ODI respectively, while neuropathic predominant pain patients experienced only 12.5%, 42.4%, and 20.9% improvement, also respectively. No neurological or infectious complications were observed acutely or during the follow-up. The present data suggests that epidural ozone might be a therapeutic option for persistent low back pain, especially in non-neuropathic predominant pain patients, but double-blind controlled studies are still required to prove its efficacy.

Keywords: pain, failed back surgery syndrome, neuropathic pain, epiduroscopy, spinal endoscopy, ozone, minimally invasive surgery

Revisões Sistemáticas

Revisões Sistemáticas

Systematic Reviews about Ozone Therapy	
Study	**Abstract**
1. CARMONA, Loreto. Revisión sistemática: ozonoterapia en enfermedades reumáticas.Ed. 3. Vol III. **Reumatol Clin**, vol. 3, p. 119-23, 2006.	**Objective:** To perform a systematic review to analyze the efficacy on which the use of ozone therapy in musculoskeletal diseases is based. **Methods:** A literature search was performed in PubMed, Embase and the Cochrane Library using highly sensitive search terms to identify all studies on ozone therapy. All studies showing the efficacy or effectiveness of ozone therapy in any musculoskeletal disease were selected. **Results:** Only 6 relevant studies were identified, 5 in lumbar disk herniation and 1 in Raynaud's syndrome. Of the 5 studies in disk herniation, only 3 were clinical trials and none used random allocation. Study participants were generally patients with symptomatic small discal hernias. There was wide variability in the dose of ozone injected as well as in the controls used for comparison. All outcome measures were subjective and there was no blinded evaluation of the results. The study in Raynaud's syndrome included only 4 patients. Adverse effects were not evaluated in detail. **Conclusions:** The use of ozone therapy in musculoskeletal diseases is based on poor quality studies. Currently, data supporting an adequate risk/benefit ratio for ozone therapy in rheumatic diseases is lacking.
2. ALBEDAH, Abdullah MN et al. Ozone therapy in postgraduate theses in Egypt: systematic review. **The Journal Of The Egyptian Public Health Association**, v. 88, n. 2, p. 57-66, 2013.	**Background:** Systematic reviews of the studies published in the major medical data bases have not shown solid support for the use of ozone therapy. Unpublished or grey literature, including postgraduate theses, may solve this controversy. **Objectives:** To review the postgraduate theses published in Egypt in order to assess the clinical safety and effectiveness of ozone therapy in specific medical conditions. **Methods:** The databases of the Egyptian Universities' Library Consortium and the databases of each university were searched for postgraduate theses that evaluated ozone therapy as an intervention for any disease or condition in any age group, compared with any or no other intervention and published before September 2010. **Results:** A total of 28 quasi trials were included. The theses did not report any safety issues in terms of ozone therapy. With respect to its effectiveness, the studies suggested some benefits of ozone in the treatment of dental infection and recovery, musculoskeletal disorders, diabetes mellitus, chronic diseases, and obstetrics and gynaecology. However, the number of studies included was small and they were of limited quality. **Conclusion**: There is insufficient evidence to recommend the use of ozone in the treatment of dental infections, in facilitating faster dental recovery after extraction or implantation, in diabetes mellitus, musculoskeletal disorders, or obstetrics and gynaecology.
3. STAAL, J. Bart et al. Injection therapy for subacute and chronic low-back pain. **Cochrane Database Syst Rev**, v. 3, n. 3, p. CD001824, 2008.	**Background:** The effectiveness of injection therapy for low-back pain is still debatable. Heterogeneity of target tissue, pharmacological agent and dosage generally found in randomized controlled trials (RCTs) points to the need for clinically valid comparisons in a literature synthesis. **Objectives:** To determine if injection therapy is more effective than placebo or other treatments for patients with subacute or chronic low-back pain.

Revisões Sistemáticas

(3.)

	Search strategy: We updated the search of the earlier systematic review and searched the Cochrane Central Register of Controlled Trials, MEDLINE and EMBASE databases from January 1999 to March 2007 for relevant trials reported in English, French, German, Dutch and Nordic languages. We also screened references from trials identified. **Selection criteria:** RCTs on the effects of injection therapy involving epidural, facet or local sites for subacute or chronic low-back pain were included. Studies which compared the effects of intradiscal injections, prolotherapy or ozone therapy with other treatments, were excluded unless injection therapy with another pharmaceutical agent (no placebo treatment) was part of one of the treatment arms. Studies about injections in sacroiliac joints and studies evaluating the effects of epidural steroids for radicular pain were also excluded. **Data collection and analysis:** Two review authors independently assessed the quality of the trials. If study data were clinically and statistically too heterogeneous to perform a meta-analysis, we used a best evidence synthesis to summarize the results. The evidence was classified into five levels (strong, moderate, limited, conflicting or no evidence), taking into account the methodological quality of the studies. **Main results:** 18 trials (1179 participants) were included in this updated review. The injection sites varied from epidural sites and facet joints (i.e. intra-articular, injections, peri-articular injections and nerve blocks) to local sites (i.e., tender- and trigger points). The drugs that were studied consisted of corticosteroids, local anesthetics and a variety of other drugs. The methodological quality of the trials was limited with 10 out of 18 trials rated as having a high methodological quality. Statistical pooling was not possible due to clinical heterogeneity in the trials. Overall, the results indicated that there is no strong evidence for or against the use of any type of injection therapy. **Authors' conclusions:** There is insufficient evidence to support the use of injection therapy in subacute and chronic low-back pain. However, it cannot be ruled out that specific subgroups of patients may respond to a specific type of injection therapy.
TORRE-AMIONE, Guillermo et al. A study to assess the effects of a broad-spectrum immune modulatory therapy on mortality and morbidity in patients with chronic heart failure: the ACCLAIM trial rationale and design. **Canadian Journal of Cardiology**, v. 23, n. 5, p. 369-376, 2007.	**Background:** Evidence has accumulated regarding the importance of inflammatory mediators in the development and progression of heart failure (HF). Although targeted anticytokine treatment strategies, specifically antitumour necrosis factor-alpha, have yielded disappointing results, this may simply reflect the redundancy of the cytokine cascade and the fact that antitumour necrosis factor-alpha therapies do not stimulate increased activity of the anti-inflammatory arm of the immune system. Ex vivo exposure of autologous blood to controlled oxidative stress and subsequent intramuscular administration is a device-based procedure shown in experimental studies to have a broad-spectrum effect on a number of immune mediators. These studies have demonstrated that this approach downregulates inflammatory cytokines, whereas several anti-inflammatory cytokines are increased. In a feasibility study of 73 patients with moderate to severe HF, active therapy (versus placebo) had a significant benefit on both mortality and hospitalization, and was not associated with adverse hemodynamic or metabolic effects. **Methods:** The Advanced Chronic heart failure CLinical Assessment of Immune Modulation therapy (ACCLAIM) trial is a multicentre, randomized, double-blind, placebo-controlled clinical trial of *New York Heart Association* functional class II to IV chronic HF patients with left ventricular ejection fraction of 30% or less. Enrolling approximately 2400 subjects at 177 sites, the primary end point of the study was the cumulative incidence (time to first event) of the combined end point of total mortality or hospitalization for cardiovascular causes. The study was completed in late 2005, when 701 primary end point events had occurred and all patients had been treated for six months.

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Revisões Sistemáticas

	Conclusions: If the ACCLAIM trial confirms earlier results, this approach represents a novel nonpharmacological treatment for HF that targets a pathogenic mechanism contributing to progression of this syndrome not addressed by current therapies.
(4.) BOCCI, Velio. The failure of the ACCLAIM tria lis due to an irrational technology. **Int. J. Cardiol**, 2008.	**Abstract** The excessive blood oxidation devised with the Celacade System does not procure any advantage in chronic heart failure's patients. The irrationality of the procedure delays a therapeutic advantage and ought to be fully revised.
5. KARAGÜLLE, MZ; KARAGÜLLE, M. Balneotherapie e Kurorttherapie rheumatischer Erkrankungen in der Türkei: Revisão Ein systematischer. **Complementary Medicine Research**, v. 11, n. 1, p. 33-41, 2004.	**Abstract** *Balneotherapy and Spa Therapy of Rheumatic Diseases in Turkey: A Systematic Review* **Aim:** Turkey has a lot of thermal and mineral springs and is looking back on a still vivid tradition of spa therapy and balneotherapy, applied especially for the treatment of rheumatic diseases. This tradition is predominantly empiric and intuitive, however, it has assumed some important aspects of modern balneotherapeutic methods as well. This article is aimed at presenting the characteristics of traditional and modern balneological and spa therapy forms in Turkey. **Method:** The studies which have been conducted between 1990 and 2000 in different spas in Turkey on the efficacy and effectiveness of spa therapy and balneotherapy for rheumatic diseases have been searched and analyzed independent of their design. A descriptive evaluation of the studies was carried out. **Results:** A total of 15 published studies have been found and analyzed. The investigations have been carried out in 8 different spa resorts in Turkey. In these studies the effectiveness and efficacy of different balneological and spa therapies on a variety of rheumatic diseases (from osteoarthritis to fibromyalgia and from rheumatoid arthritis to low back pain) could be shown. Nearly all studied balneotherapeutic modalities were applied as bathing cures. Only in one study peloid therapy was applied. Balneotherapeutic therapy was applied in a modern and traditional way, and both open and stationary spa therapy forms were used at the same time. **Conclusions:** The review has shown the effectiveness of the investigated spa therapy and balneotherapy forms. It could be concluded that nearly all forms of spa therapy and balneotherapy used for the treatment of rheumatic diseases in Turkey are effective. A definitive conclusion, however, is not possible because of the heterogeneity of the study designs, methodological flaws, and the publication bias. In future good quality randomized controlled trials are needed.
6.	

Revisões Sistemáticas

7. MAGALHAES, Francisco N. et al. Ozone therapy as a treatment for low back pain secondary to herniated disc: a systematic review and meta-analysis of randomized controlled trials. **Pain Physician**, v. 15, n. 2, p. E115-E129, 2012.	**Background:** Low back pain (LBP) is one of the most common and important health problems affecting the population worldwide and remains mostly unsolved. Ozone therapy has emerged as an additional treatment method. Questions persist concerning its clinical efficacy. **Objective:** The purpose of our study was to evaluate the therapeutic results of percutaneous injection of ozone for low back pain secondary to disc herniation. **Study Design:** A systematic review and meta-analysis of randomized controlled trials. **Methods:** A comprehensive literature search was conducted using all electronic databases from 1966 through September 2011. The quality of individual articles was assessed based on the modified Cochrane review criteria for randomized trials and criteria from the Agency for Healthcare Research and Quality. Outcome Parameters: The outcome measure was short-term pain relief of at least 6 months or long-term pain relief of more than 6 months. **Results:** Eight observational studies were included in the systematic review and 4 randomized trials in the meta-analysis. The indicated level of evidence for long-term pain relief was II-3 for ozone therapy applied intradiscally and II-1 for ozone therapy applied paravertebrally. The grading of recommendation was 1C for intradiscal ozone therapy and 1B for paravertebral ozone therapy. **Limitations:** The main limitations of this review are the lack of precise diagnosis and the frequent use of mixed therapeutic agents. The meta-analysis included mainly active-control trials. No placebo-controlled trial was found. **Conclusions:** Ozone therapy appears to yield positive results and low morbidity rates when applied percutaneously for the treatment of chronic low back pain.
8. VERHAGEN, Arianne P. et al. Balneotherapy (or spa therapy) for rheumatoid arthritis. **The Cochrane Library**, 2015.	**Background** Balneotherapy (spa therapy or mineral baths) for patients with arthritis is one of the oldest forms of therapy. One of the aims of balneotherapy is to soothe the pain, improve joint motion and as a consequence to relieve patients' suffering and make them feel well. In this update we included one extra study. **Objectives** To assess the effectiveness of balneotherapy for rheumatoid arthritis. **Search methods** We searched the following databases up to October 2006: CENTRAL (Issue 3, 2006), PubMed, CINAHL, the database from the Cochrane'Rehabilitation andRelatedTherapies'FieldandPedro.Wealsoperformedreferencecheckingandpersonal communications with authors to retrieve eligible studies. **Selection criteria** Randomised controlled trials comparing balneotherapy with any other intervention or with no intervention. Included patients were all suffering from definite or classical rheumatoid arthritis as defined by the American Rheumatism Association Criteria or by the criteria of Steinbrocker. At least one of the WHO/ILAR core set of endpoints for RA clinical trials had to be among the main outcome measures. **Data collection and analysis** Two authors independently assessed quality and extracted data. Disagreements were solved by consensus.

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Systematic Review

Ozone Therapy as a Treatment for Low Back Pain Secondary to Herniated Disc: A Systematic Review and Meta-analysis of Randomized Controlled Trials

Francisco N. De Oliveira Magalhaes, MD, Luciana Dotta, MD, Andre Sasse, PhD, Manoel J. Teixeira, MD, PhD, and Erich T. Fonoff, MD, PhD

From: Hospital das Clinicas University of Sao Paulo Medical School, Sao Paulo, Brazil.

Dr. Magalhaes is with the Reabilitation and Phisiatric Discipline, Department of Ortopedics, Hospital das Clinicas, University of Sao Paulo Medical School, Sao Paulo, Brazil. Dr. Dotta is with the Department of Surgery, Medical Sciences School, State University of Campinas - UNICAMP, Campinas, Sao Paulo. Dr. Sasse, Dr. Teixeira and Dr. Fonoff are with the Pain Center and Division of Functional, Neurosurgery Institute of Psychiatry of Hospital das Clinicas, Department of Neurology - University of Sao Paulo Medical School, Sao Paulo, Brazil.

Address correspondence: Erich T. Fonoff, M.D, PhD Pain Center and Division of Functional Neurosurgery Institute of Psychiatry of Hospital das Clinicas Department of Neurology - University of Sao Paulo Medical School Sao Paulo, Brazil E-mail: fonoffet@usp.br

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Background: Low back pain (LBP) is one of the most common and important health problems affecting the population worldwide and remains mostly unsolved. Ozone therapy has emerged as an additional treatment method. Questions persist concerning its clinical efficacy.

Objective: The purpose of our study was to evaluate the therapeutic results of percutaneous injection of ozone for low back pain secondary to disc herniation.

Study Design: A systematic review and meta-analysis of randomized controlled trials.

Methods: A comprehensive literature search was conducted using all electronic databases from 1966 through September 2011. The quality of individual articles was assessed based on the modified Cochrane review criteria for randomized trials and criteria from the Agency for Healthcare Research and Quality.

Outcome Parameters: The outcome measure was short-term pain relief of at least 6 months or long-term pain relief of more than 6 months.

Results: Eight observational studies were included in the systematic review and 4 randomized trials in the meta-analysis. The indicated level of evidence for long-term pain relief was II-3 for ozone therapy applied intradiscally and II-1 for ozone therapy applied paravertebrally. The grading of recommendation was 1C for intradiscal ozone therapy and 1B for paravertebral ozone therapy.

Limitations: The main limitations of this review are the lack of precise diagnosis and the frequent use of mixed therapeutic agents. The meta-analysis included mainly active-control trials. No placebo-controlled trial was found.

Conclusions: Ozone therapy appears to yield positive results and low morbidity rates when applied percutaneously for the treatment of chronic low back pain.

Key words: Low back pain, oxygen-ozone, ozone therapy, chronic pain, failed back surgery syndrome.

Pain Physician 2012; 15:E115-E129

Low back pain (LBP) is one of the most common and important clinical, social, economic, and public health problems affecting the human population worldwide (1). Around 70% of adults suffer from LBP at some point in their lifetime with various degrees of symptom severity. Additionally, 1.6% to 43% of these patients have LBP associated with sciatic symptoms (2). In the United States, the incidence of chronic low back pain ranges from 15% to 45%, with a prevalence of 30% (1). Most back pain has no recognizable cause

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243 Level of Evidence

The indicated level of evidence is II-3 for ozone therapy applied intradiscally and II-1 for ozone therapy applied paravertebrally on long-term relief in low back pain secondary to disc herniation (12).

Injeção Paravertebral

Injeção Intradiscal

Table 1. *Levels of evidence based on the Quality data available in the literature (USPSTF).*

I:	Evidence obtained from multiple properly conducted diagnostic accuracy studies.
II-1:	Evidence obtained from at least one properly conducted diagnostic accuracy study of adequate size.
II-2:	Evidence obtained from at least one properly designed small diagnostic accuracy study.
II-3:	Evidence obtained from diagnostic studies of uncertainty.
III:	Opinions of respected authorities, based on clinical experience descriptive studies Evidence obtained from case reports or reports of expert committees.

Adapted and modified from the U.S. Preventive Services Task Force (USPSTF)(12).

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(8.)		**Conclusions** *Implications for practice* Balneotherapyforpatients with arthritisisone of theoldestforms of therapy. We found silver level evidence of benefit of mineral baths when compared to drug treatment at 8 weeks. One cannot ignore the positive findings reported in most studies, however, thereisinsufficientevidencetosupporttheclaimsofpositivefindingsinmoststudies. Thescientificevidenceisinsufficientbecause of the poor methodological quality, the absence of an adequate statisticalanalysis, andforthepatient, theabsenceofessentialoutcome measures (pain, quality of life). *Implications for research* 1. Large, high quality research is needed, focusing on appropriate allocation concealment, blinding and an adequate data presentation and analysis. The design and reporting of future trials should conform to the CONSORT-statement. 2. New researchshould use outcome measures thatare relevantto the patients, and adequate and responsive to the treatment under study. Follow-up shouldbeof sufficientlengthtoassess long-term effects. 3. New research should provide full data on outcome measures, including the mean and standard deviation or 95% confidence interval. 4. Future research should examine the effectof balneotherapy not onlyinpragmatictrialscomparingvariousinterventionswitheach other, but also in more explanatory trials comparing the intervention with a no treatment control group. When possible, the beneficial effect of the 'spa-environment' should be considered as a confounder or effectmodifier and should be accounted for in the design of the trial. We conclude that performing randomised studies with high methodologicalqualityconcerningtheeffectivenessofbalneotherapy is both possible and necessary to provide strong evidence on the effects of balneotherapy.
9.	NÜESCH, Eveline et al. Comparative efficacy of pharmacological and non-pharmacological interventions in fibromyalgia syndrome: network meta-analysis. **Annals of the Rheumatic Diseases**, v. 72, n. 6, p. 955-962, 2013.	**Objectives** To synthesise the available evidence on pharmacological and non-pharmacological interventions recommended for fibromyalgia syndrome (FMS). **Methods** Electronic databases including MEDLINE, PsycINFO, Scopus, the Cochrane Controlled Trials Registry and the Cochrane Library were searched for randomised controlled trials comparing any therapeutic approach as recommended in FMS guidelines (except complementary and alternative medicine) with control interventions in patients with FMS. Primary outcomes were pain and quality of life. Data extraction was done using standardised forms. **Results** 102 trials in 14 982 patients and eight active interventions (tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin noradrenaline reuptake inhibitors (SNRIs), the gamma-amino butyric acid analogue pregabalin, aerobic exercise, balneotherapy, cognitive behavioural therapy (CBT), multicomponent therapy) were included. Most of the trials were small and hampered by methodological quality, introducing heterogeneity and inconsistency in the network. When restricted to large trials with ≥100 patients per group, heterogeneity was low and benefits for SNRIs and pregabalin compared with placebo were statistically significant, but small and not clinically relevant. For non-pharmacological interventions, only one large trial of CBT was available. In medium-sized trials with ≥50 patients per group, multicomponent therapy showed small to moderate benefits over placebo, followed by aerobic exercise and CBT. **Conclusions** Benefits of pharmacological treatments in FMS are of questionable clinical relevance and evidence for benefits of non-pharmacological interventions is limited. A combination of pregabalin or SNRIs as pharmacological interventions and multicomponent therapy, aerobic exercise and CBT as non-pharmacological interventions seems most promising for the management of FMS.
10.	BENDER, Tamás et al. Evidence-based hydro-and balneotherapy in Hungary—a systematic review and meta-analysis. **International journal of biometeorology**, v. 58, n. 3, p. 311-323, 2014.	Balneotherapy is appreciated as a traditional treatment modality in medicine. Hungary is rich in thermal mineral waters. Balneotherapy has been in extensive use for centuries and its effects have been studied in detail. Here, we present a systematic review and meta-analysis of clinical trials conducted with Hungarian thermal mineral waters, the findings of which have been published by Hungarian authors in English. The 122 studies identified in different databases include 18 clinical trials. Five of these evaluated the effect of hydro- and balneotherapy on chronic low back pain, four on osteoarthritis of the knee, and two on osteoarthritis of the hand. One of the remaining seven trials evaluated balneotherapy in chronic inflammatory pelvic diseases, while six studies explored its effect on various laboratory parameters. Out of the 18 studies, 9 met the predefined criteria for meta-analysis. The results confirmed the beneficial effect of balneotherapy on pain with weight

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(10.)	bearing and at rest in patients with degenerative joint and spinal diseases. A similar effect has been found in chronic pelvic inflammatory disease. The review also revealed that balneotherapy has some beneficial effects on antioxidant status, and on metabolic and inflammatory parameters. Based on the results, we conclude that balneotherapy with Hungarian thermal-mineral waters is an effective remedy for lower back pain, as well as for knee and hand osteoarthritis.
11. IBÁÑEZ-VERA, A. J.; GARCÍA-ROMERO, J. C.; ALVERO-CRUZ, J. R. Fisioterapia pasiva para el tratamiento del síndrome de fibromialgia. Una revisión sistemática. **Fisioterapia**, v. 39, n. 5, p. 216-222, 2017.	**Objectives:** To review the most recent literature on the effects of passive physiotherapy in the treatment of fibromyalgia, including the different techniques used and the measurement of their effectiveness on each symptom. **Search strategy:** a bibliographic search was carried out in PubMed database to locate clinical trials conducted in the previous five years. **Study selection:** Of the 683 studies found, 18 of them were selected and assessed according to their methodological quality using the PEDro scale. **Summary of results:** passive physiotherapy could be an effective treatment, since techniques such as electrotherapy, balneotherapy, and myofascial release improve pain and quality of life in the subjects. Depression is improved by manual therapy and balneotherapy. Transcutaneous electrical nerve stimulation (TENS) and manual therapy improve sleep. **Conclusions:** Passive physiotherapy could be an effective symptomatic treatment. The choice of the technique must depend on the specific symptom required to be treat.
12. FITZPATRICK, Erin; HOLLAND, Olivia J.; VANDERLELIE, Jessica J. Ozone therapy for the treatment of chronic wounds: A systematic review. **International wound journal**, 2018.	Chronic wounds present a significant burden to the health care system and the patient. Ozone therapy has been proposed as a treatment for chronic wounds, potentially acting by eliciting mild oxidative stress or disinfection. The purpose of this systematic review is to evaluate the potential benefits and harms of ozone therapy as an advanced care intervention for chronic wounds. Studies were extracted from Google Scholar, PubMed, the Cochrane Library, and reference lists. General inclusion criteria included English-language randomised human trials reporting the use of ozone therapy in the topical treatment of chronic wounds. Primary outcome data included the extent of chronic wound healing, and secondary outcomes included adverse effects. Studies were assessed for level of bias and data quality. Nine studies (n = 453 patients) matched the inclusion criteria and underwent meta-analysis. Overall, there was a significant improvement in wound closure with ozone therapy. Results consistently favour the application of ozone as a treatment for chronic wounds; however, there is no conclusive evidence of ozone therapy as superiores compared with standard treatments. Compared with standard care, ozone therapy as an advanced wound care treatment may improve the proportion of chronic wounds healed in a shorter amount of time, but further research is required.
13. LIU, Jian et al. Ozone therapy for treating foot ulcers in people with diabetes. 2015.	It has been reported that ozone therapy might be helpful in treating foot ulcers in people with diabetes mellitus (DM).To assess the effects of ozone therapy on the healing of foot ulcers in people with DM.In March 2015 we searched: The Cochrane Wounds Group Specialised Register, The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library), Ovid MEDLINE, Ovid MEDLINE (In-Process & Other Non-Indexed Citations), Ovid EMBASE, EBSCO CINAHL, Science Citation Index, Chinese Biomedical Literature Database and The Chinese Clinical Registry. There were no restrictions based on language, date or study setting.We included randomised controlled trials (RCTs) that compared ozone therapy with sham ozone therapy or any other interventions for foot ulcers in people with DM, irrespective of publication date or language.Two reviewers independently screened all retrieved citations, selected relevant citations and extracted data. Disagreements were resolved by discussion with a third reviewer. The methodological quality of included studies and the evidence level of outcomes were assessed using the Cochrane risk of bias tool and the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach respectively. Data were expressed using risk ratio (RR) for dichotomous outcomes and mean difference (MD) for continuous outcomes with their 95% confidence interval (95% CI). Review Manager (RevMan) software was used to analyse the data.Three

Revisões Sistemáticas

(13.)

14.

	studies (212 participants) were included in this review. The overall risk of bias was high for two trials and unclear for one. One trial (101 participants) compared ozone treatment with antibiotics for foot ulcers in people with DM. The study had a follow-up period of 20 days. This study showed that ozone treatment was associated with a greater reduction in ulcer area from baseline to the end of the study than treatment with antibiotics (MD -20.54 cm(2), 95% CI -20.61 to -20.47), and a shorter duration of hospitalisation (MD -8.00 days, 95% CI -14.17 to -1.83), but did not appear to affect the number of ulcers healed over 20 days (RR 1.10, 95% CI 0.87 to 1.40). No side effects were observed in either group. The other two trials (111 participants) compared ozone treatment plus usual care with usual care for foot ulcers in people with DM. The meta-analysis results did not show evidence of a difference between groups for the outcomes of reduction of ulcer area (MD -2.11 cm(2), 95% CI -5.29 to 1.07), the number of ulcers healed (RR 1.69, 95% CI 0.90 to 3.17), adverse events (RR 2.27, 95% CI 0.48 to 10.79), or amputation rate (RR 2.73, 95%CI 0.12, 64.42).The available evidence was three small RCTs with unclear methodology, so we are unable to draw any firm conclusions regarding the effectiveness of ozone therapy for foot ulcers in people with DM.
IKONOMIDIS, S. T. et al. Conservative treatment of acute or chronic tendinitis with oxygen-ozone mixture. A double blind clinical trial. **Rivista Italiana di Ossigeno-Ozonoterapia**, v. 2, p. 67-71, 2003.	Increasingly more medical ozone is used in the treatment of pain. So much so that recently the Spanish Ministry of Health has included ozone therapy in the portfolio of pain units. The effectiveness, safety and good tolerability of ozone, in□l-trated as well as administered systemically, justify the extent of its use in recent years. Because little is known in general on this subject, the aim of this revision is to update current knowledge about ozone therapy in pain medicine.


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http://dx.doi.org/10.1080/01919512.2016.1191992

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Ozone in Medicine: Clinical Evaluation and Evidence Classification of the Systemic Ozone Applications, Major Autohemotherapy and Rectal Insufflation, According to the Requirements for Evidence-Based Medicine

Renate Viebahn-Hänsler[a], Olga Sonia León Fernández[b], and Ziad Fahmy[a]

[a]Medical Society for the Use of Ozone in Prevention and Therapy, D-76473 Iffezheim/Baden-Baden, Germany; [b]Pharmacy and Food Institute, University of Havana, Havana, 10 400 Cuba

ABSTRACT

Now that indications are clearly defined, applications have mostly become standardized and the active mechanisms have been well confirmed, medical ozone application in the form of the low-dose concept, is established and proven as a complementary medical method in the treatment of chronic inflammations or diseases associated with chronic inflammatory conditions. More than 11,000 systemic ozone treatments in the form of Major Ozone Autohemotherapy (MAH) in 577 patients and ≥ 47,000 Rectal Insufflations (RI) in 716 patients in various clinical studies are subjected to critical clinical assessment and classification according to the criteria of evidence-based medicine (EBM). Statistically significant clinical and/or pharmacological improvements without side-effects or adverse reactions are found in all studies; special attention is drawn to maintaining hygiene when working with blood and to the use of ozone-resistent and biocompatible materials. On summarizing the evidence classification under RCT + CT (Randomized Controlled Trials + Controlled Trials), i.e., Levels Ib and IIa, 12 studies with 657 ozone-treated patients are obtained for MAH and 6 studies with 227 patients for RI. As a result of the evidence here assessed, the two systemic ozone applications, MAH and RI are part of evidence-based medicine. Both applications are effective, safe and economic.

ARTICLE HISTORY
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KEYWORDS
Evidence-Based Medicine; Major Autohemotherapy; Ozone Medicine; Rectal Insufflation

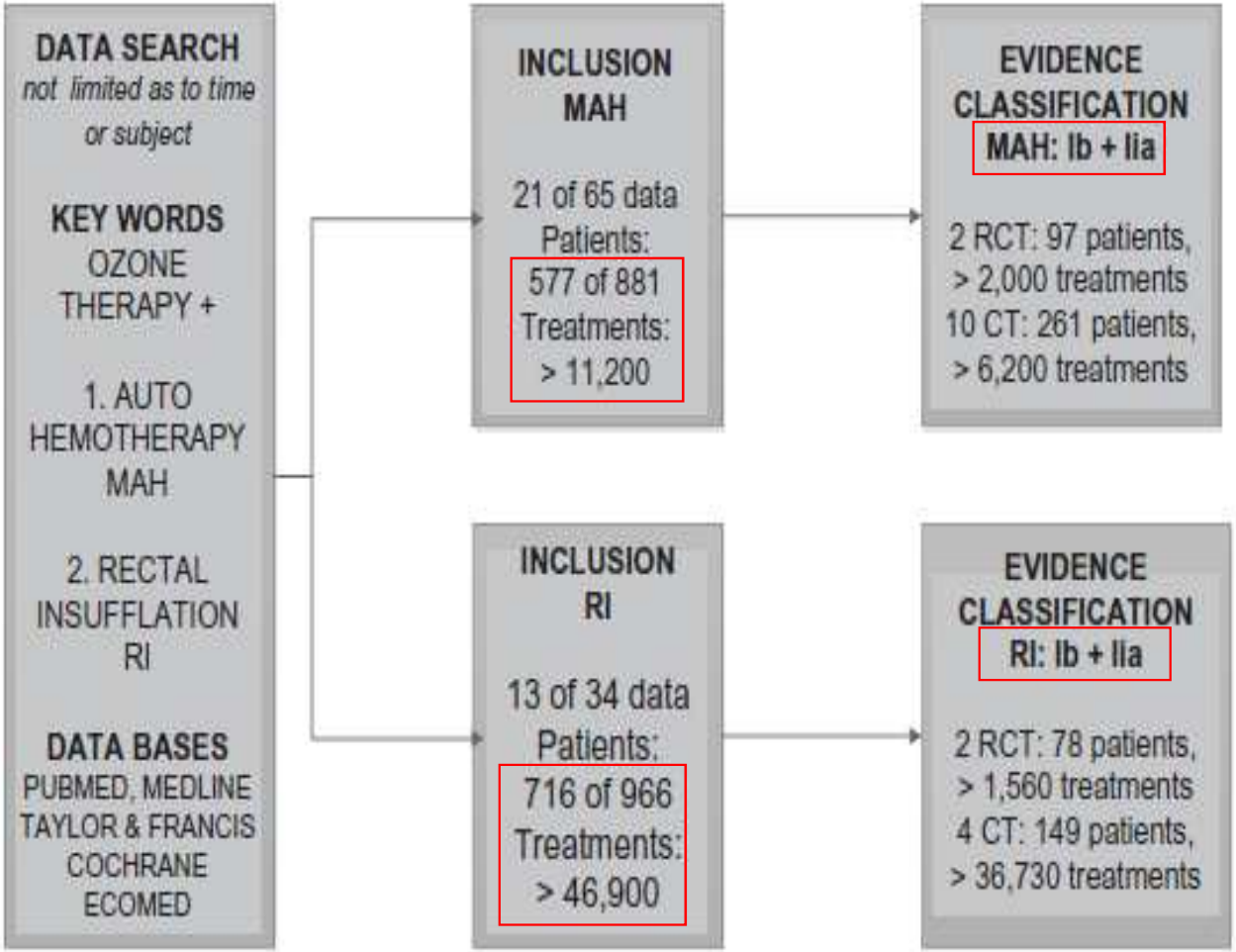

Figure 5. Results of data search and evaluation. MAH: major auto hemotherapy, RI: rectal insufflation RCT: randomized, controlled trial, CT: controlled trial.

Table 1. Levels of evidence according to Cochrane Library 1992 based on Oxford 2009.

Level	Evidence-type
Ia	At least 1 systematic review of high quality randomized controlled studies (RCTs)
Ib	At least 1 high-quality randomized controlled trial RCT
IIa	At least 1 high-quality nonrandomized trial
IIb	At least 1 high-quality trial without control group
IIIa	More than 1 high-quality controlled case study
IIIb	High quality noncontrolled case study
IV	Expert opinion as clinical experience is concerned

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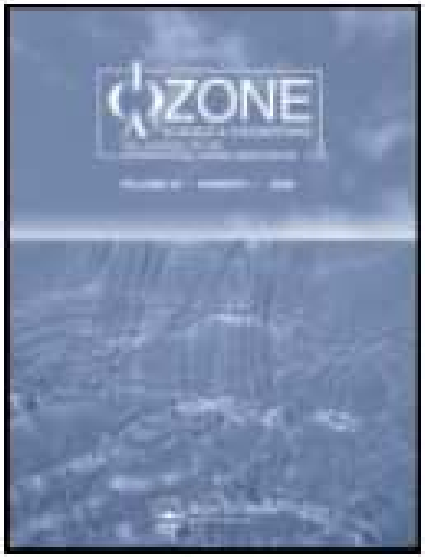
http://dx.doi.org/10.1080/01919512.2016.1191992



Ozone: Science & Engineering: The Journal of the International Ozone Association

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Ozone in Medicine: The Low-Dose Ozone Concept—Guidelines and Treatment Strategies

Renate Viebahn-Hänsler [a] , Olga Sonia León Fernández [b] & Ziad Fahmy [a]

[a] Medical Society for the Use of Ozone in Prevention and Therapy, Iffezheim/Baden-Baden, D-76473, Germany

[b] Pharmacy and Food Institute, University of Havana, Havana, 10 400, Cuba

TABLE 2. Application-Relevant Concentration and Dosage Ranges in Ozone Therapy

Application	Ozone Concentration Range	Ozone Volume	Dosage/Ozone Amount Per Treatment
Systemic Treatment			
Major autohemotherapy (MAH)	10–30 µg/ml (max. 40 µg/ml)	50 ml	500–1,500 µg (max. 2000)
Rectal insufflation	10–25 µg/ml	max. 300 ml	3,000–7,500 µg
Minor autohemotherapy	10–20 µg/ml	10 ml	100–200 µg
Topical Treatment			
Wound cleansing	80–100 µg/ml		
Wound healing	10–25 µg/ml		
Injections in pain Syndrome	1–10 µg/ml	1 ml–20 ml	1–200 µg
In combination with local anesthetic	10–20 µg/ml	1 ml–20 ml	10–400 µg

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Ozone in Medicine: The Low-Dose Ozone Concept—Guidelines and Treatment Strategies

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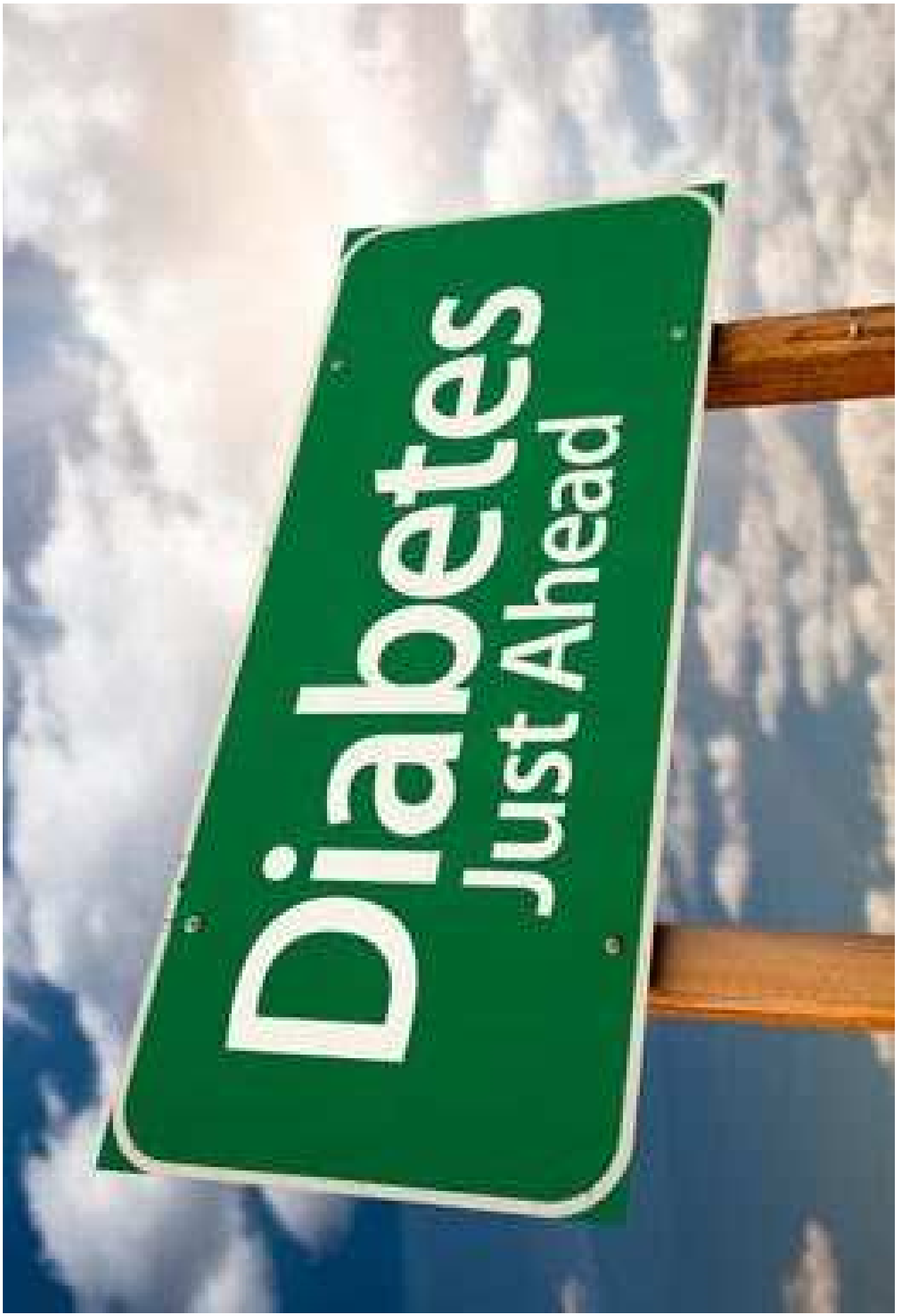
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Pré-ozônio

Pós-ozônio

Estudos comprovaram que o tratamento com ozônio medicinal acelera o tempo de cicatrização das feridas de diabetes. Por isso, **a Ozonioterapia diminui o tempo de internação, bem como o uso de medicamentos, e inclusive a probabilidade das amputações entre 45 a 95%.**

Cláudia Cardoso

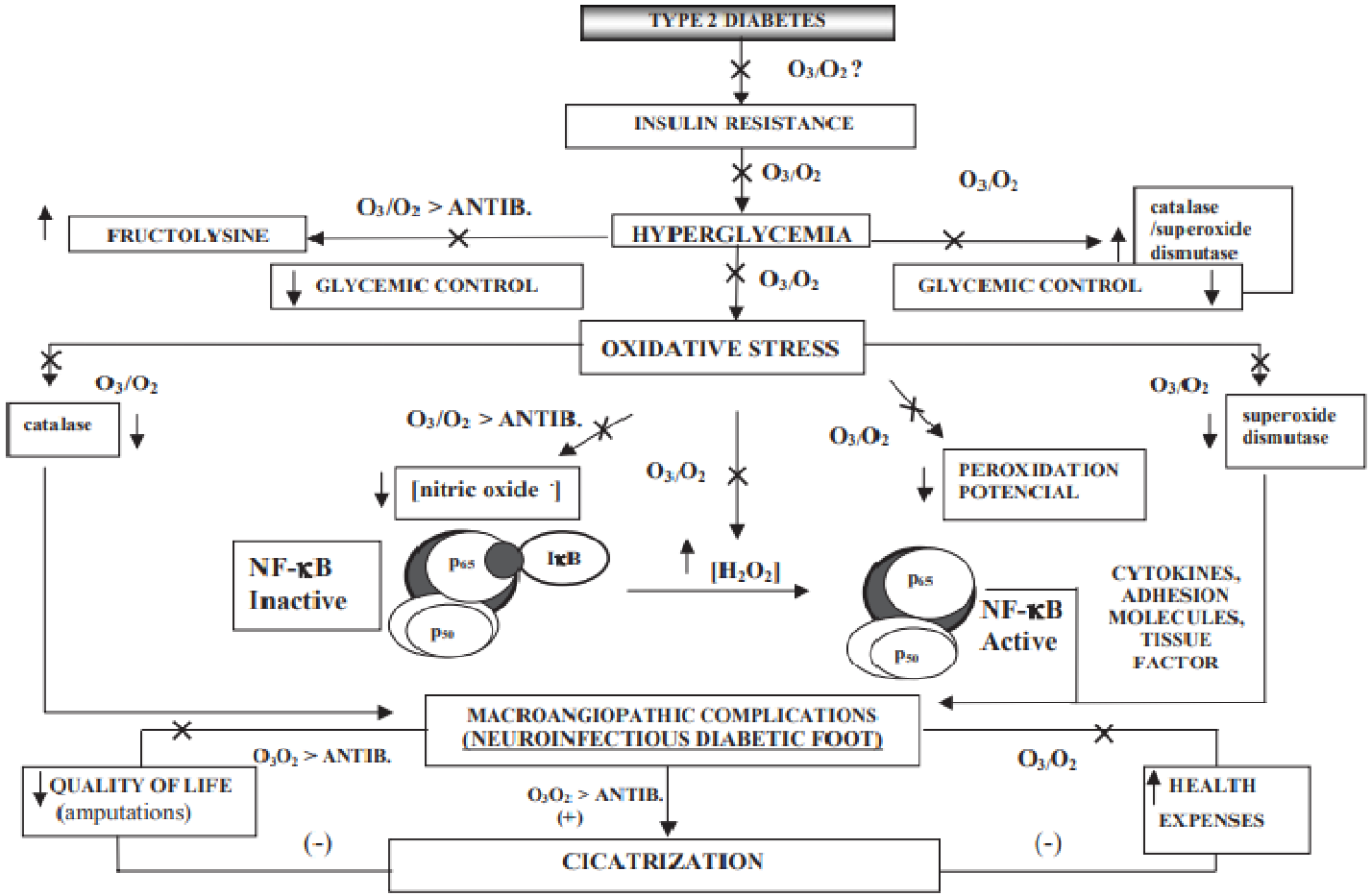

Fig. 2. Events associated with diabetes, its complications and its relation with ozone therapy in the different stages of the pathological cascade. Legend: Pathways blocked by the use of ozone (X), pathways probably blocked by the use of ozone (?), increase (↑), decrease (↓), inhibition (−), activation (+). Ozone treatment improved glycemic control, prevented oxidative stress, standardized organic peroxide levels, and activated superoxide dismutase. The pharmacodynamic effect of ozone in the treatment of patients with neuroinfectious diabetic foot can be ascribed to the possibility of its being a superoxide scavenger.

Perspectivas do Diabetes no Brasil

	2010	2030
DIABÉTICOS	7,6 MILHÕES	12,7 MILHÕES
AMPUTAÇÕES	228 MIL	381 MIL
CUSTO TOTAL DO SUS COM DIABETES	R$ 6 BILHÕES	R$ 10 BILHÕES
CUSTO TOTAL DO SUS COM DIABETES E OZONIOTERAPIA	R$ 5,1 BILHÕES	R$ 8,5 BILHÕES

COBERTURA TOTAL DO AUMENTO DA DEMANDA COM OZONIOTERAPIA

REDUÇÃO DE 18% NO ORÇAMENTO DA SAÚDE PÚBLICA COM OZONIOTERAPIA

Fonte: IBGE e Ministério da Saúde


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Research Article

Medical Ozone Reduces the Risk of γ-Glutamyl Transferase and Alkaline Phosphatase Abnormalities and Oxidative Stress in Rheumatoid Arthritis Patients Treated with Methotrexate

Gabriel Takon Oru[1], Renate Viebhan-Haensler[2], Gilberto López Cabreja[3], Irainis Serrano Espinosa[3], Beatriz Tamargo Santos[1], Juan Carlos Polo Vega[1], Susana Sánchez Cintas[3] and Olga Sonia León Fernández[1]*

[1]Pharmacy and Food Institute, University of Havana, Cuba
[2]Department of Ozone, Medical Society for the Use of Ozone in Prevention and Therapy, Germany
[3]Department of Rheumatology, National Institute of Rheumatology, Cuba

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***Corresponding author**

Olga Sonia León Fernández, Pharmacy and Food Institute, University of Havana, 222 St #21425, Coronela. Lisa. Havana 13 603, Cuba, Tel: (537) 7272 7726; Email: olga@infomed.sld.cu

Keywords Medical ozone; Methotexate; γ -Glutamyl trasnsferase; Oxidative

Abstract

Background: Methotrexate (MTX) + Medical Ozone increase MTX clinical efficacy in Rheumatoid Arthritis (RA) patients.

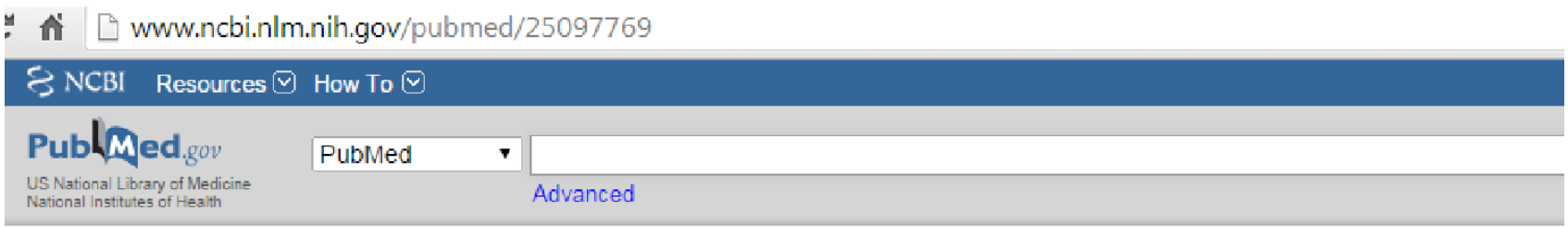
Aim: The purpose of this study was to investigate whether medical ozone could decrease the risk of γ -Glutamyl Trasnsferase (GGT), Alkaline Phosphatase (ALP) abnormalities and oxidative stress in RA patients.

Methods: A prospective study with 100 patients was performed, who were divided into two groups: one (n = 50) treated with MTX, Folic acid and Ibuprophen (MTX Group) and the second group (n = 50) receiving the same as the MTX Group + medical ozone by rectal insufflation. The diagnosis of RA patients was performed using Anti-Cyclic Citrullinated Peptides levels, DAS-28 and HAQ-DI. The risk of liver marker abnormalities and the oxidative stress were evaluated by means of biochemical methods and statistical tests.

Results: MTX + Ozone reestablished γ-Glutamyl Trasnsferase (GGT), reduced Alkaline Phosphatase (ALP), enhanced the antioxidants endogenous and decreased oxidative damage to biomolecules with regard to MTX monotherapy. Patients treated with MTX + medical ozone decreased the risk of GGT and ALP abnormalities by a factor of 4. An inverse correlation between GGT and reduced glutathione was found.

Conclusions: MTX + Ozone regulated and decreased the risk of GGT and ALP abnormalities. The modulation of GGT by ozone and the reduction of oxidative stress may play an important role against liver damage induced by MTX.


Ozonioterapia reduz
os efeitos colaterais da
Radioterapia e Quimioterapia
e melhora a qualidade de vida.



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Sultan Qaboos Univ Med J. 2014 Aug;14(3):e342-8. Epub 2014 Jul 24.

Ozone-Oxidative Preconditioning Prevents Doxorubicin-induced Cardiotoxicity in Sprague-Dawley Rats.

Delgado-Roche L[1], Hernández-Matos Y[1], Medina EA[1], Morejón DÁ[1], González MR[2], Martínez-Sánchez G[3].

Author information

Abstract

OBJECTIVES: Induced dilated cardiomyopathy is the main limitation of the anti-cancer drug doxorubicin, which causes oxidative stress and cardiomyocyte death. As ozone therapy can activate the antioxidant systems, this study aimed to investigate the therapeutic efficacy of ozone-oxidative preconditioning against doxorubicin-induced cardiotoxicity.

METHODS: The study was carried out from September 2013 to January 2014. Sprague-Dawley rats were randomly distributed in the following treatment groups: Group 1 were treated with 2 mg/kg intraperitoneal (i.p.) of doxorubicin twice a week for 50 days; Group 2 were treated with 0.3 mg of ozone/oxygen mixture at 50 µg/mL of ozone per 6 mL of oxygen by rectal insufflation and then treated with doxorubicin; Group 3 were treated as Group 2 but only with the oxygen, and Group 4 were treated with oxygen first, and then with sodium chloride i.p. as the control group.

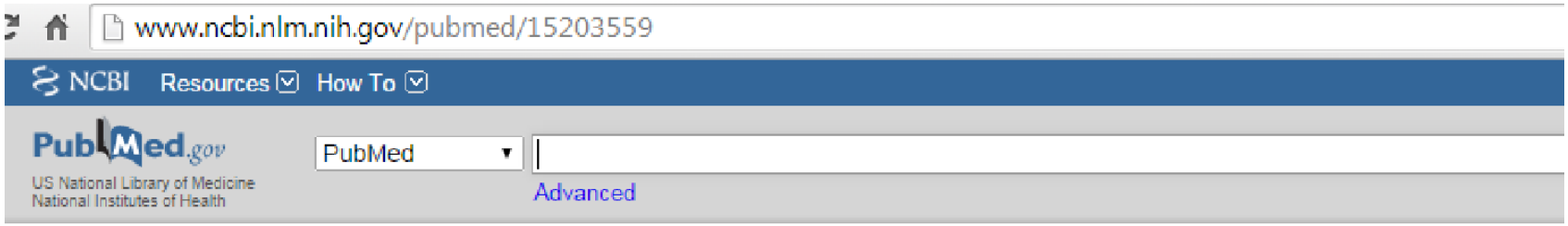
RESULTS: The results showed that ozone therapy preserved left ventricle morphology which was accompanied by a reduction of serum pro-brain natriuretic peptide levels. The cardioprotective effects of ozone-oxidative preconditioning were associated with a significant increase ($P < 0.05$) of antioxidant enzymes activities and a reduction of lipid and protein oxidation ($P < 0.05$).

CONCLUSION: Ozone-oxidative preconditioning prevents doxorubicin-induced dilated cardiomyopathy through an increase of antioxidant enzymes and a reduction of oxidised macromolecules. This establishes the background for future studies to determine if ozone therapy can be used as a complementary treatment for attenuating doxorubicin-induced cardiotoxicity in cancer patients.

KEYWORDS: Cardiotoxins; Dilated Cardiomyopathy; Doxorubicin; Oxidative Stress; Ozone

PMID: 25097769 [PubMed] PMC4117659 Free PMC Article

Cardiotoxicidade



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Complicações de Quimioterapia

Mediators Inflamm. 2004 Feb;13(1):13-9.

Protection by ozone preconditioning is mediated by the antioxidant system in cisplatin-induced nephrotoxicity in rats.

Borrego A[1], Zamora ZB, González R, Romay C, Menéndez S, Hernández F, Montero T, Rojas E.

Author information

Abstract

BACKGROUND: Acute renal failure is a dose-limiting factor of cisplatin chemotherapy. Here, we show the protective effect of ozone oxidative preconditioning against cisplatin-induced renal dysfunction in rats. Ozone oxidative preconditioning is a prophylactic approach, which favors the antioxidant-pro-oxidant balance for preservation of the cell redox state by increasing antioxidant endogenous systems in various in vivo and in vitro experimental models.

AIMS: To analyze the protective role of ozone oxidative preconditioning against cisplatin-induced nephrotoxicity.

METHODS: Male Sprague-Dawley rats were pretreated with 15 intrarectal applications of ozone/oxygen mixture at 0.36, 0.72, 1.1, 1.8 and 2.5 mg/kg before cisplatin intraperitoneal injection (6 mg/kg). Serum and kidneys were extracted and analyzed 5 days after cisplatin treatment for determinations of the renal content of glutathione, thiobarbituric acid-reactive substances, renal concentration and enzymatic activities of catalase, superoxide dismutase and glutathione peroxidase.

RESULTS: Ozone pretreatment prevented the increase in serum creatinine levels, the glutathione depletion and the inhibition of superoxide dismutase, catalase and glutathione peroxidase activities induced by cisplatin in the rat kidney. Also, the renal content of thiobarbituric acid-reactive substances was decreased by ozone therapy. These protective effects of ozone were dose dependent.

CONCLUSIONS: Intrarectal ozone therapy prevented effectively the renal antioxidant unbalance induced by cisplatin treatment.

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Clin Invest Med. 2013 Feb 1;36(1):E9-17.

Effects of ozone therapy on cyclophosphamide-induced urinary bladder toxicity in rats.

Tasdemir S, Tasdemir C, Vardi N, Ates B, Taslidere E, Karaaslan MG, Sapmaz HI, Sagir M, Kurt A, Baser CA.

Department of Pharmacology, Medical Faculty, Inonu University, Malatya, Turkey. sedamd23@gmail.com

Abstract

PURPOSE: This study investigated the efficacy of ozone therapy (OT) in a rat model of cyclophosphamide-induced hemorrhagic cystitis (HC).

METHODS: Forty Wistar Albino male rats were divided into five groups: sham, OT, cyclophosphamide (CP), OT+CP and CP+OT. Hemorrhagic cystitis (HC) was induced by intraperitoneal (i.p) administration a single dose of 100 mg/kg CP. OT was performed once daily for three days. The CP+OT group received OT (0.2 mg/kg) i.p 24 h after CP administration. CP was injected to the OT+CP group the day after the third course of OT. All animals were killed four days after CP administration. Bladder injury and oxidative stress parameters were determined from tissue samples.

RESULTS: We found small, but non-statistically significant biochemical and histological changes in the animals treated with OT alone. CP administration induced cystitis, as manifested by a marked loss of urothelial cells, as well as hemorrhaging and edema in the bladder as determined by histopathological examination. It also caused a significant decrease in the endogenous antioxidant compound glutathione (GSH) and elevation of lipid peroxidation, and nitric oxide (NO) and myeloperoxidase (MPO) levels in the rats' urinary bladder tissue. OT was able to ameliorate these changes; however these effects were prominent in the CP+OT group when compared with the OT+CP group.: For example, the NO level in the CP+OT group was 68% of the OT+CP group ($p < 0.05$).

CONCLUSION: OT prevented CP-induced urothelial damage by diminishing bladder oxidative stress, inflammation and NO levels. OT may help to ameliorate bladder damage induced by CP in the clinical setting.

PMID: 23374601 [PubMed - in process]

Ileíte por Quimioterapia

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Research Paper

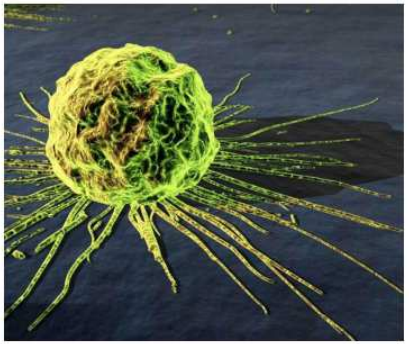
Ozone ameliorates methotrexate-induced intestinal injury in rats

Vural Kesik,* Bulent Uysal, Bulent Kurt, Erol Kismet and Vedat Koseoglu

Department of Pediatric Oncology; Gulhane Military Medical Faculty; School of Medicine; Etlik, Ankara Turkey

Key words: methotrexate, ozone therapy, intestinal injury, lipid peroxidation, liver and kidney injury, oxidant stress, mucositis

Methotrexate (Mtx) is an effective chemotherapeutic agent used in various cancer treatments. Gastrointestinal toxicity is the drug's major limiting factor, arising mainly from oxidative damage. It has been proposed that ozone (O_3) is an activator of antioxidant enzymes. Thus, this study was designed to investigate the efficacy of ozone therapy in the prevention of Mtx-induced intestinal injury in rats. Twenty rats were allocated into three groups: sham, Mtx alone (untreated) and Mtx + O_3 (treated with ozone). Ozone was administered at a dose of 0.72 mg/kg daily via an intraperitoneal route for 15 d. On d 16, Mtx was applied via an intraperitoneal injection at a dose of 6 mg/kg for 5 d. All rats were sacrificed at d 21. Efficacy of the treatment was assessed by measuring the histopathologic injury score (HIS), and biochemically by determining tissue superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and malondialdehyde (MDA) in ileum, liver and kidney homogenates. Although two rats (25%) died in the untreated group, all rats in the sham and treatment groups survived the study. The HIS, antioxidant enzyme and MDA levels of the ileal tissue were significantly lower in the ozone treated group than the untreated group ($p < 0.05$). Although the antioxidant enzyme and MDA levels of liver and kidney were significantly lower in the ozone treated group ($p < 0.05$), there was no significant change in histopathology ($p > 0.05$). Thus, ozone preconditioning shows a preventative effect in the ileum by decreasing tissue damage and increasing antioxidant enzyme activity in an experimental model of Mtx-induced intestinal injury.



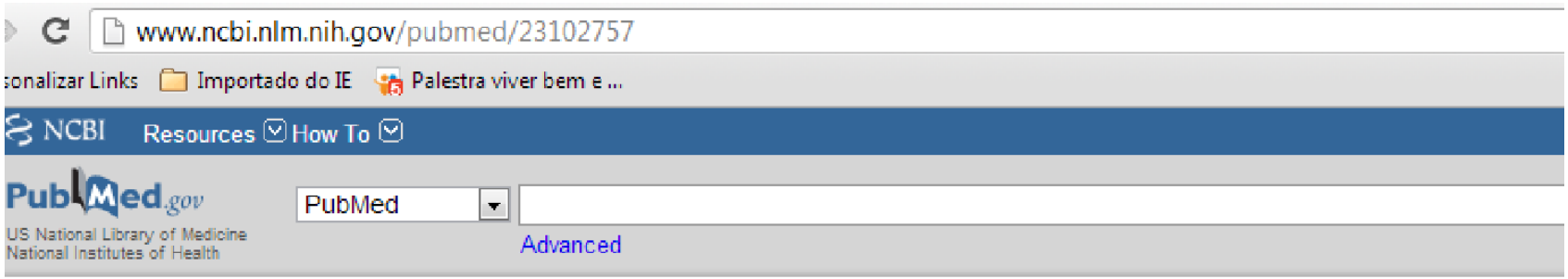
Complicações de Radioterapia

THE JOURNAL OF ALTERNATIVE AND COMPLEMENTARY MEDICINE
Volume 11, Number 3, 2005, pp. 539–541

Intravesical Ozone Therapy for Progressive Radiation-Induced Hematuria

BERNARDINO CLAVO, M.D.,[1–4] DOMINGA GUTIÉRREZ, R.N.,[1] DIONISIO MARTÍN, M.D.,[5] GERARDO SUÁREZ, R.N.,[1,3] MARÍA A. HERNÁNDEZ, M.D.,[1,3] and FRANCISCO ROBAINA, Ph.D.[2,3]

Hematúria Actínica



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J Pain Symptom Manage. 2012 Oct 26. pii: S0885-3924(12)00402-2. doi: 10.1016/j.jpainsymman.2012.06.017. [Epub ahead of print]

Long-Term Control of Refractory Hemorrhagic Radiation Proctitis With Ozone Therapy.

Clavo B, Ceballos D, Gutierrez D, Rovira G, Suarez G, Lopez L, Pinar B, Cabezon A, Morales V, Oliva E, Fiuza D, Santana-Rodriguez N.

Radiation Oncology Department, Dr. Negrin University Hospital, Las Palmas, Spain; Chronic Pain Unit, Dr. Negrin University Hospital, Las Palmas, Spain; Experimental Surgery-Research Unit, Dr. Negrin University Hospital, Las Palmas, Spain; Canary Islands Institute for Cancer Research (ICIC), Las Palmas, Spain; Grupo de Investigación Clínica en Oncología Radioterápica (GICOR), Madrid, Spain. Electronic address: bernardinoclavo@gmail.com.

Abstract

CONTEXT: Persistent or severe hemorrhagic radiation proctitis (HRP) has limited therapeutic options.

OBJECTIVES: To describe our experience with ozone therapy (O(3)T) in the management of refractory HRP.

METHODS: Patients (n=17; median age 69 years [range 42-80 years]) previously irradiated for prostate or uterine cancer and suffering persistent or severe HRP without response to conventional treatment were enrolled to receive an O(3)/O(2) gas mixture via rectal insufflations and topical application of ozonized oil. Most of the patients (83%) had Grade 3 or Grade 4 toxicity. Median follow-up post-O(3)T was 40 months (range 3-56 months).

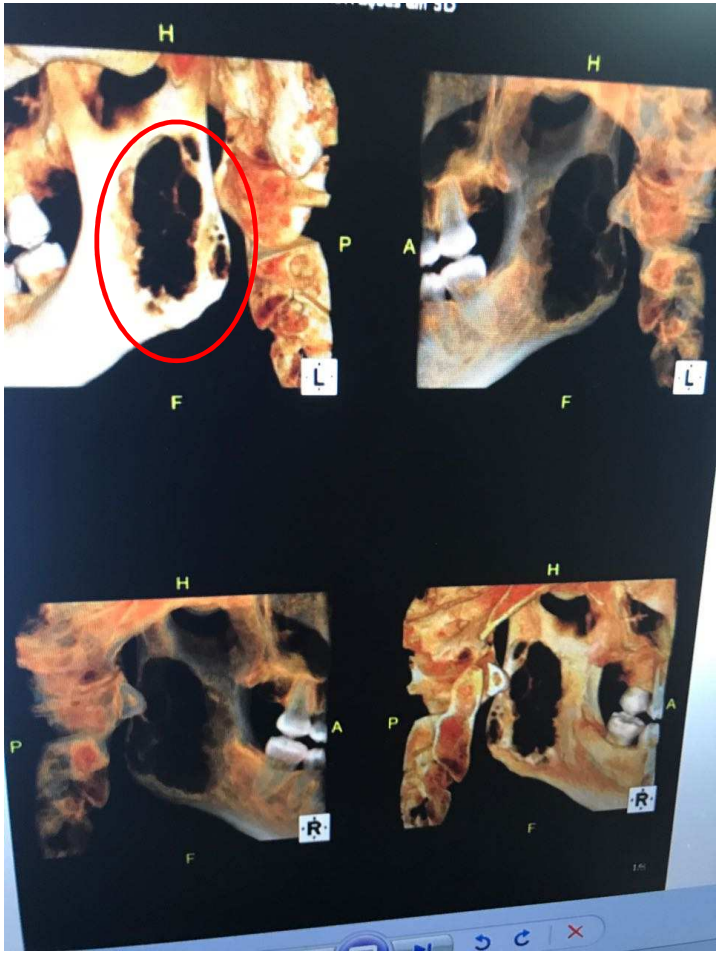
RESULTS: Endoscopic treatments required were 43 (median 1; range 0-10) pre-O(3)T, 17 (median 0; range 0-8; P=0.063) during O(3)T, and five (median 0; range 0-2; P=0.008) during follow-up. Hemoglobin levels were 10.35g/dL (7-14g/dL) pre-O(3)T and 13g/dL (9-15g/dL) (P=0.001) post-O(3)T. Median toxicity grades were 3 (range 2-4) pre-O(3)T, 1 (range 0-2; P<0.001) at the end of O(3)T, and 0 (range 0-1; P<0.001) at the last follow-up.

CONCLUSION: Persistent advanced HRP was significantly improved with O(3)T. The addition of O(3)T can be useful as a complementary treatment in the long-term management of HRP and, as such, merits further evaluation.

PMID: 23102757 [PubMed - as supplied by publisher]

Proctite Actínica

LinkOut - more resources



Mieloma Múltiplo,
Dezembro de 2016

Mieloma Múltiplo,
Setembro de 2017
Após Quimioterapia
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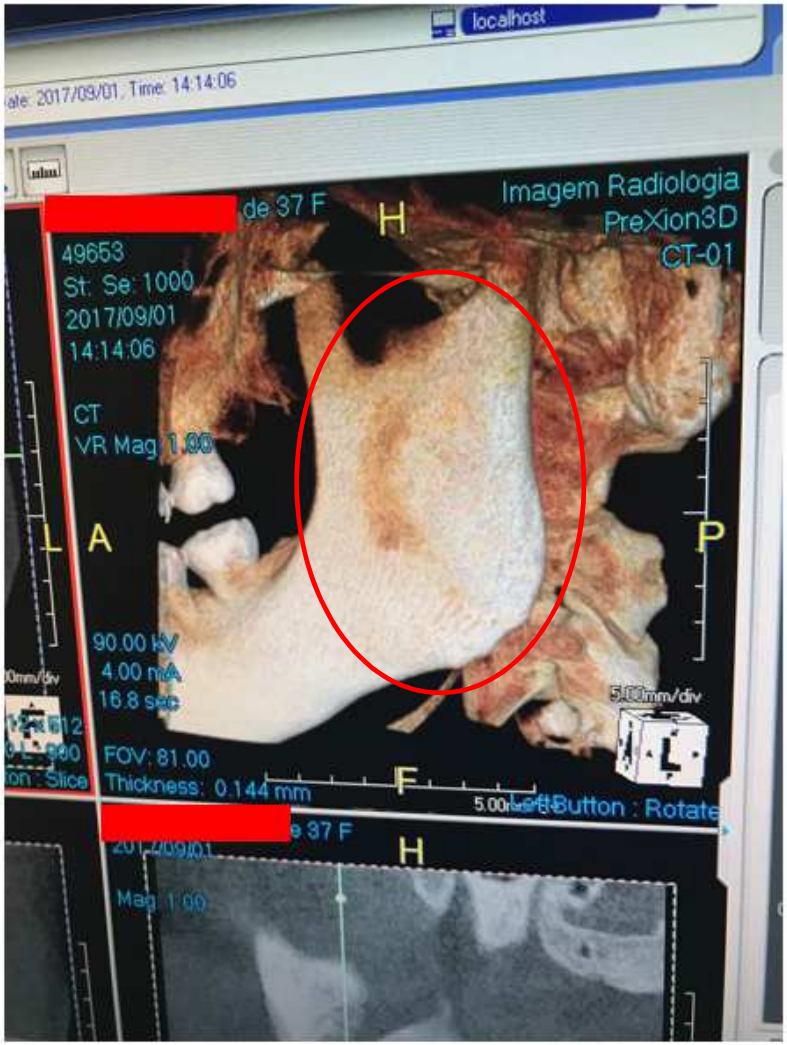
de Medula Óssea
+
Ozonioterapia
(sistêmica +
Injeções locais)

9 meses



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Mother's Milk-Induced Hsp70 Expression Preserves Intestinal Epithelial Barrier Function in an Immature Rat Pup Model

JENNIFER L. LIEDEL, YUEE GUO, YUEYUE YU, SHENG-RU SHIOU, SANGZI CHEN, ELAINE O. PETROF, SHIEN HU, MARK W. MUSCH, and ERIKA C. CLAUD
Departments of Pediatrics [J.L.L., Y.G., Y.Y., S.-R.S., S.C., E.C.C.] and Medicine [S.H., M.W.M., E.C.C.], The University of Chicago, Chicago, Illinois 60637; Department of Medicine [E.O.P.], Queen's University, Kingston, Ontario K7L 2V7, Canada

Abstract

Preterm infants face many challenges in transitioning from the *in utero* to extrauterine environment while still immature. Failure of the preterm gut to successfully mature to accommodate bacteria and food substrate leads to significant morbidity such as neonatal necrotizing enterocolitis. The intestinal epithelial barrier plays a critical role in gut protection. Heat shock protein 70 (Hsp70) is an inducible cytoprotective molecule shown to protect the intestinal epithelium in adult models. To investigate the hypothesis that Hsp70 may be important for early protection of the immature intestine, Hsp70 expression was evaluated in intestine of immature rat pups. Data demonstrate that Hsp70 is induced by exposure to mother's milk. Hsp70 is found in mother's milk, and increased Hsp70 transcription is induced by mother's milk. This Hsp70 colocalizes with the tight junction protein ZO-1. Mother's milk-induced Hsp70 may contribute to maintenance of barrier function in the face of oxidant stress. Further understanding of the means by which mother's milk increases Hsp70 in the ileum will allow potential means of strengthening the intestinal barrier in at-risk preterm infants.

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Mediators of Inflammation
Volume 2007, Article ID 26785, 6 pages
doi:10.1155/2007/26785

Research Article

Ozonation of Human Blood Induces a Remarkable Upregulation of Heme Oxygenase-1 and Heat Stress Protein-70

Velio Bocci, Carlo Aldinucci, Francesca Mosci, Fabio Carraro, and Giuseppe Valacchi

Department of Physiology, University of Siena, 53100 Siena, Italy

Correspondence should be addressed to Velio Bocci, bocci@unisi.it

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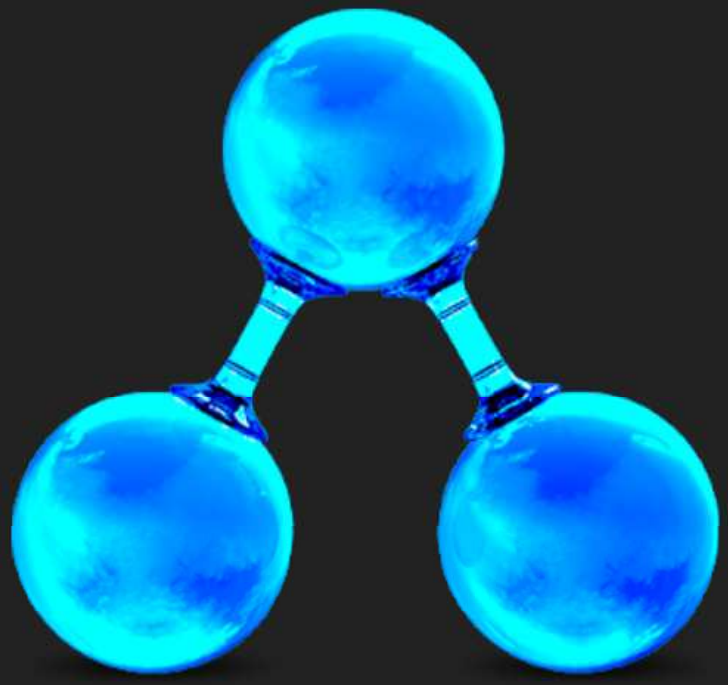
Heme oxygenase-I (HO-1) has emerged as one of the most protective enzymes and its pleiotropic activities have been demonstrated in a variety of human pathologies. Unpublished observations have shown that HO-1 is induced after the infusion of ozonated blood into the respective donors, and many other experimental observations have demonstrated the efficacy of oxidizing agents. It appeared worthwhile to evaluate whether we could better define the activity of potential inducers such as hydrogen peroxide and ozonated human plasma. Human vascular endothelial cells at confluence were challenged with different concentrations of these inducers and the simultaneous production of nitric oxide (NO); and HO-1 was measured by either measuring nitrite, or bilirubin formation, or/and the immune reactivity of the protein by Western blot using a rabbit antihuman HO-1 and Hsp-70. The results show that production of both NO and HO-1 is fairly dose dependent but is particularly elevated using human plasma after transient exposure to a medium ozone concentration. At this concentration, there is also induction of Hsp-70. The results clarify another positive effect achievable by the use of ozone therapy.

Ozonioterapia atua de forma semelhante ao leite materno...

Ozonioterapia gera qualidade de vida.

Eficácia (Evidências Científicas)



Segurança

Custo-Benefício

A Ozonioterapia ou Oxigênio-Ozonioterapia, à semelhança da Oxigenioterapia Hiperbárica, utiliza um gás medicinal eficaz e seguro.

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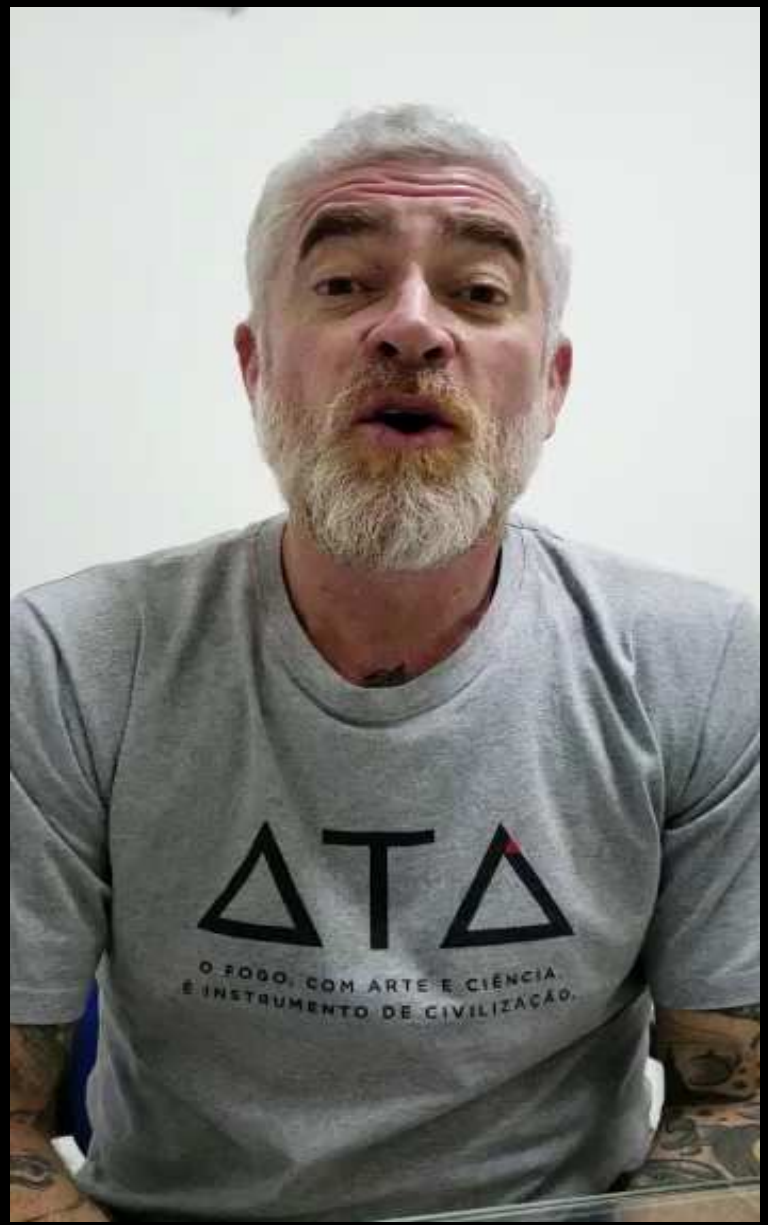
4. As empresas que fabricam gases medicinais são reguladas pela Anvisa?
5. Orientações Específicas aos Fabricantes de Gases Medicinais


ΔTΔ
O FOGO, COM ARTE E CIÊNCIA,
É INSTRUMENTO DE CIVILIZAÇÃO.

A Ozonioterapia é uma técnica que SEGURAMENTE interessa à população brasileira !

emilia.gadelha1@gmail.com
ozonizadosdobrasil@gmail.com