



Review paper

Analgetic effect of ozone therapy: myths of reality?

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ABSTRACT

Introduction: Administration of an oxygen-ozone mixture is one of the innovative techniques used in single-drug or complex therapeutic schemes for treatment of many degenerative-dystrophic pathologies of the musculoskeletal system and related neurological complications.

Aim: The aim was to determine the mechanisms of physiological action of the oxygen-ozone mixture in order to substantiate its efficacy for treatment of chronic pain syndrome with underlying degenerative-dystrophic pathologies of the musculoskeletal system.

Material and methods: The article covers biochemical and pathomorphological studies that explain the mechanism of the pain syndrome and the potential effect of the ozone therapy.

Results and discussion: The treatment schemes and benefits of different routes of ozone administration (intramuscularly, intravenously, intradiscally and intraarticularly) were analyzed. Diverse research data demonstrated influence on the causes of chronic pain, pathophysiological phases, and possible complications. The prospects of further studies for development of the most effective techniques for treatment of various pain syndromes were assessed.

Conclusions: Ozone therapy is one of the alternative rehabilitation methods with a substantial pain relieving effect. As of today, the possibility of using the oxygen-ozone mixture for treatment of chronic back pain related to intervertebral disk hernia and fibromyalgia has been substantially confirmed.

1. INTRODUCTION

Pain syndrome is one of the distinct pathological demonstrations, which significantly reduces the quality of life of patients, and contributes to the emergence of a significant medical and socioeconomic problems at the state level.^{1–3} By occurrence, it occupies a leading position among other syndromes and is a clinical result of many acute and chronic pathologies.^{4–8}

Chronic pain with the incidence of 56% is one of the most common pain syndromes in general medical practice, which explains its leading position among main causes of decline, or even loss of ability to work.^{8,9} The results of 70 randomized and 19 cohort studies conducted in the United States and Europe, involving 1,134 patients and 653 retrospectively evaluated cases, showed that chronic pain occurs in 40%–80% of the population during the course of a lifetime^{2,10} – 24% of men and 32% of women suffer from chronic dorsalgia between 20 and 64 years of age.¹¹

Approaches to treatment of pain syndrome are quite controversial. Inadequate therapy results in a direct recurrence of the syndrome. Doctors of various specialties are highly interested in finding new approaches to mitigating the intensity of the pain.

2. AIM

The aim was to analyze the biochemical and pathophysiological grounds of pain syndrome and to assess the efficacy of ozone therapy for treatment of chronic pain associated with fibromyalgia.

3. MATERIAL AND METHODS

The arguments presented in this article are the result of numerous independent studies conducted globally. Of particular interest is the experimental data obtained from testing laboratories, animal models and clinical experience. Studies of chronic pain syndromes at the biochemical level and their pathogenetic course made it possible to explain the effect of the ozone therapy in more detail. The possibility of administering an oxygen-ozone mixture for achieving an antioxidative effect, restoration of the immune response balance, and synthesis of biologically active substances (BAS) allowed to reliably determine the expedience of using this technique in the therapy of chronic fibromyalgia.

3.1. Pain syndrome theory and its biochemical background

Research has shown that neuropathic pain syndromes arise from the damage to structures associated with the nociceptive pathway.^{12,13} The neuropathic pain syndrome is characterized by polymorphism consisting of persistent or paroxysmal pain, sensory deficit in the pain area, allodynia, hyperalgesia and hyperpathia.^{11,14,15}

It has been found that an adequate afferent input of nociceptive impulse from the periphery is accurately controlled by an inhibitory system. Theories suggest that pathological pain develops when the inhibitory mechanisms of the dorsal horns, namely, T-neurons, are incapacitated.

There are two main types of pain receptors: the first one is the free nerve endings, the irritation of which causes dull and diffused chronic pain. Another type is represented by complex pain receptors, which, when excited, produce acute and localized pain. BAS, called allogeneic compounds, synthesized in pathological foci irritate receptors.^{16–18} These compounds include biogenic amines, products of local immune responses, cellular inflammation and disintegration. It has been found that interleukins are one of the first BASs to appear at the site of inflammation. They are synthesized by both macrophages and endothelial cells.¹⁹

High concentrations of prostaglandins (PGs) are also reported in the areas of acute and chronic inflammation. The chemical bonds in PGs molecules are unstable, and thus they produce short and local effect. However, synergism with other BASs (histamine, serotonin, bradykinin, and cytokines) contributes to the migration of neutrophils to the inflammation site, causing a persistent pain syndrome. Moreover, *in vitro* experiments demonstrated that PG₂ were able to inhibit T- and B-lymphocytes, implying their ability to cellular and humoral protection of the human body.^{20,21}

In addition, there exists a natural antinociceptive system, which controls the activity of the structures that receive, conduct and analyze pain signals. It has been demonstrated that 3 h after the onset of the inflammation or damage to the peripheral tissues there develops a compensatory amplification of the opioid system and inhibitory spinal pathways, which exert their effects through γ -aminobutyric acid (GABA) receptors and α 2-adrenoceptors.²²

It should be noted that GABA neurotransmitter is one of the main CNS inhibitory neurotransmitters. About 30%–40% of CNS synaptic contacts were found GABAergic. The complex mechanism contributes to the control of the nociceptive impulse transmission at all levels; therefore, a disturbance of this control may lead to the deterioration of pain sensitivity.⁴

3.2. Modern treatment landscape

Neutralization of products of biochemical reactions, namely the elimination of excessive accumulation of inflammatory mediators, such as prostaglandins, histamine and other BAS in tissues, is considered a pathophysiologically substantiated pain syndrome treatment option.^{23,24}

Conservative therapies involve administration of painkillers from both nonsteroidal anti-inflammatory drugs (NSAIDs) and muscle relaxants.²⁵ Continuous administration of such medications leads to a number of predicted undesirable iatrogenic diseases. Physical and psychological addiction of patients that were administered long-term opioid painkillers and central muscle relaxants raises certain concerns.²⁶ Such issues constitute form a base for a long-lasting discussion on daily doses and length of therapy.

Alternative medicine, often referred to as physiotherapy, has a conservative effect on the pathological process. Application of various physical factors (direct and impulse current, magnetic field, laser irradiation, etc.) for pain mitigation have shown credible results. The benefits of physiotherapy consist of an insignificant number of contraindications, absence of age restrictions, and a reasonable cost. Alternative medicine techniques are one of the important components of a rehabilitation process that help patients to return to their normal lifestyle, even after a surgical treatment. For some time, physiotherapeutic treatment was overshadowed by the traditional medicine. However, the growing number of drug-related side effects, patients' overload, comorbidities, and a long-running chronic pain syndrome have objectively justified the use of alternative medical methods in combination with traditional ones. Such combination of methods makes it possible to utilize an individual step-by-step approach to solving complex clinical problems.

3.3. Ozone therapy mechanism

Ozone is a safe and active low-cost chemical substance. The paradox of this chemical substance is in its ability to exert both oxidative and antioxidant properties. The ozone molecule is characterized by approx. 10 times greater solubility in liquids than oxygen, explaining its rapid diffusion in blood and penetration in tissues.¹⁵ An active antioxidant buffer system is formed in the human body due to chemical interaction of ozone with different chemical compounds.^{26,27} The result of the reaction is the formation of biomolecules that play important anti-inflammatory and analgesic roles for their antioxidant effect.²⁸

Contact of ozone with biological tissues results in formation of peroxides and activation of glutathione system, which contributes to the improvement of the oxygen transport. The energy supply of cells improves through stimulation of ATP synthesis. Growing intracellular content of the energetic substance provides the tissue with metabolic protection and reduces stimulation of BAS pain receptors.^{29–31} These systems explain the major proliferative mechanisms of the ozone therapy.^{25,32} At the same time, specific reactions on phospholipids of leukocyte and erythrocyte cell membrane lead to an antiadhesive phenomenon and significantly reduce the activity of molecules involved in the formation of thrombi.^{25,33} The phenomenon of leukocyte adhesion reduction is used for preventing white blood clot formations.

For example, ozone therapy optimizes hemorheological parameters and improves tissue oxygenation, which is especially pronounced in patients with coronary heart disease. Positive changes in the blood's rheological properties make it possible to further understand the features of ozone therapy and its effect on microcirculation, and to explain the possibility of administration of oxygen-ozone mixture for diminishing ischemia and areas of hypoxia.³⁴ Practical use of the method on patients with peripheral ischemic disorders and underlying diabetes mellitus showed an analgesic effect and, in most cases, prevented limb amputations.³⁵

The influence of ozone on neutralization of malonic dialdehyde as one of the main lipid peroxidation products was shown. The biochemical component of ozone therapy is demonstrated not only in relation to lipids but also in acceleration of carbohydrate and protein metabolism. The use of ozone therapy helps to stabilize sugar levels in patients with diabetes mellitus and to reduce manifestations of endothelial dysfunction.^{8,30,33,36}

In addition, one of the unique features of ozone therapy is modulation of immune response of the patient's body.^{31,37} The analgesic effect of ozone in infectious inflammation is achieved through a direct inhibitory action against various types of bacteria, viruses and fungi. These microorganisms cannot sustain the stress inflicted by ozone, resulting in their destruction, fragmentation and exertion.³⁸ The indirect bactericidal effect is exerted through metabolic changes caused by the oxygen-ozone mixture. The final antimicrobial effect of the ozone therapy lies in activation of specific antibodies.³⁹

The theoretically predicted major analgesic effect of ozone was confirmed on biological models. Subcutaneous administration of oxygen-ozone mixture to mice (a neuropathic pain model) prevented the emergence of allodynia and reduced the concentration of pro-inflammatory enzymes in the orbitofrontal cortex.⁴⁰ Fuccio et al. (2009) showed that ozone therapy protected cells from apoptosis.⁴¹

Published scientific data suggests that a significant decrease in the concentration of inflammatory cytokines and their precursors in the area of artificial peripheral nerve injury is caused by subcutaneous injection of oxygen-ozone mixture.⁴¹ Injection of ozone into knee joints of rats (rheumatoid arthritis model) resulted in a significant decrease in production of inflammatory and pain-driving biochemical substances, such as tumor necrosis factor α (TNF- α) and TNF- α receptor 2 – not observed in the control group. Also, a number of studies on laboratory animal models confirmed the activity of the ozone atom in reduction of concentration of inflammatory mediators – TNF- α , interleukins (IL) 1 β and IL-6.^{40,42,43}

It is important to highlight another specific feature of the ozone therapy demonstrating its uniqueness. Ozone is rapidly deactivated with subsequent production of active ozonides.^{30,31,41} At excessive concentrations, the latter can cause cytotoxic and cytolytic effects.^{44,45} To avoid the harmful effect, international protocols must be used for treatment of diseases using ozone therapy which focus, among others, on a careful calculating of the ozone dosage.

For treating an acute and chronic pain syndrome, ozone is administered intraarticularly, intramuscularly, intravenously, subcutaneously, and even directly in intervertebral discs (intradiscally).^{28,45,46} The routes of oxygen-ozone mixture administration may vary over the course of the treatment depending on the features of the pain syndrome and the disease course.

3.4. Clinical effect of ozone therapy

In most cases, the ozone technique is used for treatment of poorly curable chronic diseases with insufficient and unstable efficacy of conventional treatment regimens. One of

these pathologies is fibromyalgia (FM). FM prevalence in the world is ranging 4%–8% of the general population, with the majority of female patients (7–10 : 1) aged 25–50 years.⁴⁷

As a nosological unit, this disease has been included in the international classification of diseases relatively recently, and there exist only a limited number of references to clinical cases in the scientific literature and recommended treatment regimens. However, the first FM clinical case was described more than 150 years ago. FM is characterized by absence of clear diagnostics and treatment criteria. Clinicians Yunus and Masi described a certain pattern of development of dominant complaints, such as chronic muscle pain syndrome associated with trigger points (pain elicited by pressure on trigger points), unreasonable weakness, and sleep disorders. The latter can be periodically combined with other symptoms that diversify the clinical picture of FM, including signs of depression, impaired ability to work, poor concentration of attention, decreased ability to learn and memorize. Therefore, disease manifestations may differ a lot and, as a rule, medicament treatment is a time-consuming process without a guaranteed long-lasting remission.^{14,47}

3.5. Why do so many pathological manifestations exist?

Clinical studies identified the pathogenetic features that cause the development of diverse disease symptoms resistant to treatment. The symptoms included alteration of the central nervous system that developed in the course of a stable pain impulse, impaired functioning of the hypothalamic-pituitary system, and excessive cytokine level.²¹ Having summarized available findings, researchers Ozgocmen et al. (2006) and Cordero (2011) independently concluded that the main role in FM development belonged to a chronic oxidative stress.^{13,48} The latter influenced the metabolism of muscle tissue and, as a result, pain and the increased muscle tone.^{13,21} Biochemical disorders included the accumulation of the enzyme peroxidase on muscle cell membrane lipids, which, in turn, boosted the oxidative stress and completed formation of the pathological cycle.

FM patients presented with an excessive malondialdehyde concentration and reduced concentration of antioxidative enzymes (catalase, glutathione peroxidase and superoxide dismutase).^{48,49} On the other hand, the disturbance of lipid peroxidation and lipoprotein accumulation were associated with the development of unreasonable weakness, another typical symptom of fibromyalgia. The stable high level of lipid metabolites explains the chronic fatigue syndrome.¹³ Subsequently, these changes in the patient's body lead to depression.¹⁴

On the other hand, Altindag and Celik (2006) found that excessive cytokine level caused the development of major FM symptoms. For example, high blood concentration of IL-6 and IL-8 appeared to stimulate the sympathetic nervous system. Laboratory studies confirmed that high IL-8 levels were indeed associated with pain, while IL-6 concentration grew in cases of hyperalgesia, excessive fatigue, and depression.¹⁵

A team of scientists led by Balestrero (2017) presented evidence of the efficacy of ozone therapy for treatment of FM patients. They used treatment regimen based on Scientific Society of Oxygen Ozone Therapy Protocol (SIOOT), which involved influencing the process with the due account to pathogenetic features of FM. Their work stressed the fact that the lack of efficacy and short-term effect of medicinal therapy were associated with the negative points of the previous treatment courses administered to the patients.⁴⁶

The topicality of ozone therapy for treatment of FM patients was substantiated by recognition of efficacy of this method not only for correcting the effects of oxidative stress, but also for restoring the functional capacity of the antioxidant system and modulating the immune response of the patient's body.^{14,20,21}

The condition for participating in the study was compliance of symptoms with fibromyalgia survey questionnaire (FSQ) and fibromyalgia impact questionnaire-revised (FIQR) scoring recommended by the American College of Rheumatology.^{49,50} The widespread pain index, the symptoms severity scale, and the commonly accepted visual analogue scale (VAS) were used to determine the treatment efficacy. The study design involved 12 daily sessions of intravenous ozone therapy. Administration of large auto-hemotherapy with a gradual increase of ozone concentration from 30 mg/mL to 50 mg/mL was alternated with low auto-hemotherapy and rectal insufflation. One month after the treatment, the subjective and objective ozone therapy efficacy data was obtained, which in all cases was statistically significant. After the completion of the trial, no adverse effects of ozone therapy were reported, which was consistent with the results obtained by other researchers.^{14,21,47}

However, the weak point of the clinical study was insufficient number of patients, which complicated the evaluation of the efficacy of the method for FM treatment. Given the pathogenetic features and diversity of clinical variants of the disease, it is believed that the ozone therapy is one of the most reasonable ways of correcting the biochemical changes in the human body that underlie development of the pathological condition. The planned promising directions of the research include the optimization of administration of the ozone therapy protocol with identification of the most effective concentration of ozone mixture, administration routes, and the development of combined therapeutic regimens.

3.6. Prospects for further studies

Along with a detailed study of pain syndrome mechanisms at pathophysiological and biochemical levels, and the details of the physiological action of the ozonous oxygen mixture, the question of the technique for administering ozone therapy remains open.

The recommended topics for further studies include finding the most effective gas mixture concentration and clinical stages of different nosologies (acute, sub-acute or chronic) at which the treatment should be commenced.

The question of the possible correlation between the pain syndrome severity and the effective concentration of active substance for ozone therapy also remains open.

4. CONCLUSIONS

Ozone therapy is an effective method of treatment that promotes scientific dialogue between traditional and alternative medicine. Recent recommendations based on research and observations on the use of ozone therapy in clinical practice are quite clear. Ozone therapy is recommended for treatment of FM – the disorder that challenging to diagnose. The reliability of the positive results in the treatment of patients with degenerative-dystrophic spine diseases by intramuscular, paravertebral, or perforaminal administration has been shown (level of evidence 1.B). The results presented in the article are based on the data from global medical researches, which demonstrate the expediency of using the ozonated mixture in managing pain syndromes stemming from traumatological and neurological diseases.

Conflict of interest

Authors declare no conflicts of interests.

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