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# Synergistic Action in Pain Therapy: An Observational Study on the Combined Use of Oxygen-Ozone Therapy and Oral and Topical Nutraceutical Supplementation

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## ABSTRACT

**Introduction:** Chronic musculoskeletal pain, often resistant to conventional treatments, negatively impacts patients' quality of life. In recent years, multimodal and integrative approaches have gained increasing importance in managing this condition. Oxygen-ozone therapy and the use of nutraceutical supplements have been recognized as emerging strategies in pain treatment.

**Objective:** To evaluate the synergistic efficacy of the combination of oxygen-ozone therapy and topical and oral nutraceutical supplementation in reducing pain symptoms, exploiting the anti-inflammatory, analgesic, and regenerative properties of ozone and the ability of nutraceutical supplementation to induce healing processes.

**Materials and Methods:** Prospective observational study conducted on 54 patients with chronic musculoskeletal pain, treated with an average of 10 sessions of oxygen-ozone therapy on a weekly basis via paravertebral or intra-articular injections and selected nutraceutical supplements administered orally for oxidative stress and for improving sleep quality and anxiety symptoms, and topically for a local analgesic and anti-inflammatory action. Pain assessment was performed using a Visual Analogue Scale (VAS). A quality-of-life questionnaire (SF-36) was administered to assess the physical, mental, and emotional impact of this intervention in patients with chronic musculoskeletal pain.

**Results:** A statistically significant reduction in mean VAS scores was observed at the end of treatment, with a mean reduction of 65% ($p<0.001$). Quality of life questionnaires showed significant improvement in domains related to pain, mobility with functional limitations in daily life and work, and to mental and emotional state.

**Conclusions:** The integrated treatment with oxygen-ozone therapy and oral and topical nutraceutical supplementation showed efficacy and good tolerability in the management of chronic musculoskeletal pain, suggesting that new personalized therapeutic models, oriented towards the integration of traditional and complementary medicine, can be exploited for patients suffering from pain.

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## Introduction

Chronic pain management represents a significant clinical challenge, requiring a complex and personalized approach: it's not just about "suppressing" the pain, but also about improving quality of life and preventing further deterioration. Chronic pain is pain that lasts more than three months or persists beyond the healing of the initial cause [1]. Chronic pain treatment is mainly symptom-based or disease-based, however, the goal is not only to reduce pain but also to increase autonomy, well-being, and improve the body's functional abilities through an integrated, multimodal approach. Currently, the management of chronic pain can start from lifestyle modification, with weight loss, physical exercise, balance diet, and smoking cessation, to drug therapies (including opioid and non-opioid treatments), psycological interventions and/or other procedures [1].

An innovative approach is the use of oxygen-ozone therapy showing beneficial anti-inflammatory and analgesic effects, with a high safety profile. Oxigen-ozone therapy use is growing for treatment of pathologies that present aspects of chronic hypoxia, inflammation, and redox imbalance, as in these cases medical ozone showed efficacy. Oxigen-ozone therapy is based on a mixture of oxygen and ozone ($O_2$-$O_3$) gases which triggers different mechanisms of action in cells [2,3].

The Main Mechanisms of Action of Ozone Therapy are based on Several Well-Known Principles:

- Modulation of oxidative stress: the $O_2$-$O_3$ mixture induces an adaptive antioxidant response by stimulating the production of protective enzymes such as glutathione peroxidase, superoxide dismutase, and catalase, reducing free radical damage.
- Improvement of cellular metabolism: the ozone improves oxygen utilization at the mitochondrial level, increasing ATP production, reducing chronic fatigue and asthenia;
- Analgesic and anti-inflammatory effect: the production of pro-inflammatory cytokines is reduced, the production of anti-inflammatory cytokines is increased, and central sensitization is reduced;
- Modulation of the immune system: possible immunomodulatory effect, very useful in subjects with autoimmune comorbidities;
- Effects on microcirculation: the ozone improves peripheral circulation, promoting tissue oxygenation and reducing muscle ischemia;
- Neuroendocrine effect: some studies suggest a positive influence on the release of endorphins and neurotransmitters (such as serotonin and dopamine) [3-7].

The above-descripted mechanisms can be synergistically improved by the treatment with nutraceutical supplementation oral and topical that can support regenerative processes and modulate the inflammatory response.

Several findings reported that ozone therapy up regulated the antioxidant defense system, counteracting the oxidative stress produced from the inflammatory mediators on glutathione antioxidant pathway [7,8]. This let us hypotizing that nutraceutical antioxidant supplementation can be added in a protocol of oxigen-ozone therapy. The most important endogenus antioxidant is glutathione, a tripeptide composed of glutamate, cysteine, and glycine that neutralizes free radicals and reactive oxygen species (ROS), protecting cells from oxidative damage [9,10]. It helps regenerate other antioxidants, such as vitamin C and vitamin E, maintaining them in their active form. In the liver, it is essential in conjugation processes (phase II of detoxification), binding to toxic substances to make them more water-soluble and facilitate their elimination. It also participates in the regulation of cell proliferation, apoptosis, and the immune response. Finally, it helps maintain mitochondrial function, which is essential for energy production and the prevention of cell death [10-13].

Glutathione can influence pain perception and modulation through various biological mechanisms related to oxidative stress, inflammation, and nerve function:

- Glutathione neutralizes free radicals, preventing nerve cell damage, reducing neuronal hyperexcitability, and peripheral and central sensitization;
- It regulates the production of pro-inflammatory cytokines (TNF-α, IL-1β), increasing anti-inflammatory cytokines: the reduction of this response reduces the stimulation of nociceptive fibers;
- In neuropathic pain secondary to chronic musculoskeletal disorders, oxidative stress damages myelin and axons: glutathione protects neurons and supports nerve regeneration, reducing the pathological transmission of pain signals, both by decreasing the activation of ion channels such as TRPV1 and NMDA, which amplify pain, and by improving the sensitivity of GABAergic or endogenous opioid receptors and strengthening natural analgesia mechanisms.

Glutathione does not act as an Immediate Pain Reliever but:

- Reduces Inflammation;
- Protects and Stabilizes Nerve Pathways;
- Prevents Nociceptive Sensitization;
- Improves the response to Endogenous and Exogenous Analgesics.

These effects make it suitable for patients with chronic inflammatory or neuropathic pain [9-13].
Glutathione effect can be increased by its combination with other nutraceutical active ingredients with strong antioxidant properties such as N-acetylcysteine, Coenzyme Q, Vitamin E and Vitamin D, along with minerals like magnesium, selenium, zinc, and copper [11, 14-21].

Another useful intervention for mitigate chronic pain is nutraceutical supplementation with compounds that can improve sleep quality and decrease anxiety symptoms. Combination therapy with natural extracts of Ashwagandha (*Withania somnifera*), Lemon Balm (*Melissa officinalis*), Passionflower (*Passiflora incarnata*), Valerian (*Valeriana officinalis*), Melatonin showed efficacy in improving sleep quality, reducing anxiety, relaxing muscles, and alleviating agitation [22-31].

This Combination can work through a multifactorial approach, combining:

- Neurotransmitter modulation (GABA, serotonin, dopamine);
- Mood support;
- Reduction of oxidative stress;
- Muscle and cognitive relaxation effects.

The use of topical remedies can also support the management of chronic pain, and several innovative topical treatment are arising in the market, in addition to traditional antiflammatory drugs. A new topical composition based on Cannabis sativa oil enriched in Cannabidiol (CBD), escin, bromelain, Boswellia extract, glucosamine sulphate, MethylSulfonylMethane (MSM) and methylsalicylate, formulated as lipogel or foam (Cibides lipogel® or Cibides spuma®) has been designed for local treatment of inflammatory and painful conditions affecting joints, muscles, tendons and/or ligaments. This formulation already showed efficacy in pain reduction in patients with localized pain related to acute minor musculoskeletal conditions and to osteoarthritis [32,33].

CBD has a complex mechanism of action and does not act directly as an agonist on the classic cannabinoid receptors CB1 and CB2, of wich is an allosteric modulator. CBD exerts numerous effects by modulating various biological systems:

- Indirectly modulates the endocannabinoid system;
- Acts on other receptors: serotonin receptors, responsible for the anxiolytic and antidepressant effect; TRPV1 receptors involved in pain perception and thermoregulation; PPAR-gamma receptors involved in inflammation and lipid and glucose metabolism; GPR55 receptors, which have antiepileptic and neuroprotective effects [34].

As consequence, the properties of CBD are:

- Anti-inflammatory properties; the inflammation is a major cause of pain, especially in conditions like arthritis. If inflammation can be reduced, CBD can help relieve the associated pain and discomfort.
- Modulation of pain signaling; CBD can influence the transmission of pain signals. It interacts with vanilloid receptors (TRPV1), associated with pain perception and

inflammation. Through this interaction, CBD can help regulate pain signaling and reduce the perception of pain.

- Modulation of endocannabinoids; CBD affects the levels of endocannabinoids, compounds naturally present in our body. By inhibiting the enzymes responsible for the degradation of endocannabinoids, CBD can increase their availability and thus potentially prolong their pain-modulating effect [34].

CBD is non-psychoactive and has a good tolerability profile, but it can interact with other drugs metabolized by the liver. It showed topical efficacy in several setting, like musculoskeletal pathologies, osteoarthritis, and peripheral neuropathies [33,35,36].

This observational study aims to explore the synergistic efficacy of two therapeutic strategies, evaluating the effect of the combined use of oxygen-ozone therapy and nutraceutical supplementation in pain management, and analyzing data from a clinical observation of patients treated in an outpatient setting.

## Materials and Methods

This is a prospective observational study conducted between November 2023 and October 2024 at the following specialist outpatient clinics: Fleming Hospital in Pontinia (LT), San Michele Hospital in Aprilia (LT), and Ecomed Center in Latina. Fifty-four patients (average age 65, 43 women and 11 men) were selected, suffering from chronic localized pain (neck pain, low back pain, knee pain, painful shoulder) lasting more than 3 months and with secondary neuropathy. The inclusion criteria were: age over 18 years, presence of chronic musculoskeletal pain, signed informed consent. The exclusion criteria were represented by the main contraindications to oxygen-ozone therapy: pregnancy, favism, and treated hyperthyroidism.

Patients received an average of 10 sessions of oxygen-ozone therapy (from a minimum of 7 to a maximum of 12 sessions) on a weekly basis via paravertebral or intra-articular injection routes at concentrations varying between 12 and 18 µg/ml. At the same time, for oxidative stress the patients were treated with Glutathione in combination with N-acetylcysteine, Coenzyme Q, Homotaurine, Vitamin E and Vitamin D, and minerals including magnesium, selenium, zinc, and copper (Gludat®, AQMA Italia S.p.A, Milan, Italy) containing 250 mg of glutathione, 1 tablet a day, in the morning, and for improving sleep quality with a combination of natural extracts of Ashwagandha (*Withania somnifera*) 200 mg/tab, Lemon Balm (*Melissa officinalis*) 80 mg/tab, Passionflower (*Passiflora incarnata*) 80 mg/tab, Valerian (*Valeriana officinalis*) 80 mg/tab, Melatonin (1 mg/tab), group B vitamins and minerals (Ansivor®, AQMA Italia S.p.A, Milan, Italy), 1 tablet a day administered 20 minutes before sleeping. The patients were also topically treated with a gel/foam formulation based on Cannabis sativa oil enriched in CBD, escin, bromelain, Boswellia extract, glucosamine sulphate, MethylSulfonylMethane (MSM) and methylsalicylate (Cibides lipogel® or Cibides spuma®, AQMA Italia S.p.A. Milan, Italy) two times a day in the morning and in the evening. Oral and topical therapies lasted until the last session of ozone therapy (about 2 months). The patients were informed of the study procedures and provided written informed consent. Local ethic boards approved the protocol. The study was conducted in accordance with the Declaration of Helsinki guidelines regarding ethical principles for medical research involving human subjects.

Pain symptoms were monitored using a 10 cm Visual Analog Scale (VAS) at time 0 (T0), at mid-cycle (T1), and at the end of treatment (T2). The VAS scale is a highly sensitive diagnostic test: it can detect small changes in pain intensity and allows for continuous monitoring of its progress. The results obtained from the VAS scale can be used to measure the percentage reduction in pain as a means of comparing treatments or monitoring the progress of pain therapy. In addition, a quality-of-life questionnaire (SF-36) was administered to assess the physical, mental, and emotional impact in patients with chronic musculoskeletal pain and to determine how these factors impact their personal perception of quality of life.

The collected data were analyzed using SPSS software. Paired-sample t-tests or ANOVA for repeated measures were used to compare the mean VAS values at the three time points. The significance level was set at $p<0.05$.

## Results

Of the 54 enrolled patients, 51 completed the treatment and 3 dropped out of the study after 3 sessions. The mean VAS score went from 8.2 +/- 1.3 (T0) to 2.9 +/- 1.0 (T2) with a mean reduction of 65% ($p<0.001$) (**Figure 1**).

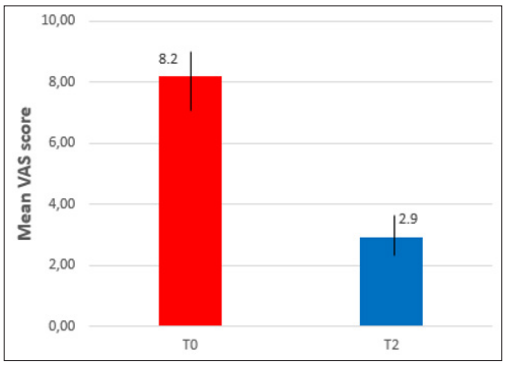


**Figure 1:** Mean Reduction of VAS Score from T0 (Pre-Treatment) to T2 (After-Treatment) in 51 Treated Patients. Standard Deviation was showed as Error Bars.

Quality of life questionnaires showed significant improvement in domains related to pain, mobility with functional limitations in daily life and work, and to mental and emotional state.

Pain perception and limitation of mobility were showed respectively in **Figure 2 and 3**, at time T0 (panel A) and T2 (panel B).

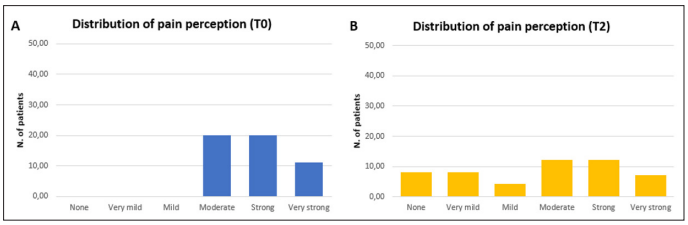


**Figure 2:** Changes in the Distribution of Pain Perception in Patients (N=51) Enrolled in the Study in the Pre-Treatment Period (T0, panel A) and Post-Treatment Period (T2, panel B).

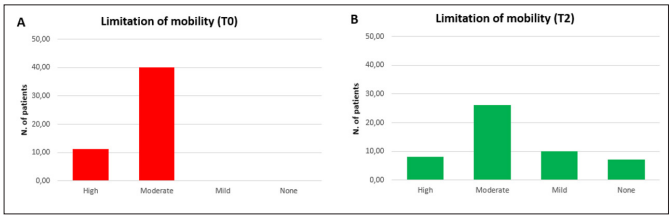


**Figure 3:** Changes in the Degree of Mobility Limitation in Patients (N=51) Enrolled in the Study in the Pre-Treatment Period (T0, panel A) and Post-Treatment Period (T2, panel B).

In Tables 1 and 2 data about the perception of the psycho-emotional health status were reported respectively pre-treatment (T0) and post-treatment (T2).

Overall, no adverse effects were reported with either oxygen-ozone therapy or oral administration of nutraceutical supplements. Some patients reported mild redness at the site of topical application, which resolved spontaneously.

**Table 1: Perception of Psycho-Emotional Health in Patients (N=51) Enrolled in the Study, in the Pre-Treatment Period (T0)**.

| Psycho-emotional state | Always | Almost always | Most of the time | Part of the time | Almost never | Never |
|---|---|---|---|---|---|---|
| Full of energy | | | | | | |
| Calm and serene | | | | | | |
| Tired | 30 | 4 | | | | |
| Exhausted | 15 | 2 | | | | |

**Table 2: Perception of Psycho-Emotional Health in Patients (N=51) Enrolled in the Study, in the Post-Treatment Period (T2).**

| Psycho-emotional state | Always | Almost always | Most of the time | Part of the time | Almost never | Never |
|---|---|---|---|---|---|---|
| Full of energy | | | | | | |
| Calm and serene | | | | | | |
| Tired | | | | 10 | 17 | 7 |
| Exhausted | | | | 2 | 11 | 4 |

## Discussion

This observational study originates from the assumption that the combination of oxygen-ozone therapy and nutraceutical supplementation, administered systemically and topically, can produce a synergistic effect in reducing chronic pain.

The nutraceutical supplement based on glutathione in combination with N-acetylcysteine, coenzyme Q, homotaurine, vitamin E and vitamin D, and minerals including magnesium, selenium, zinc, and copper (Gludat®, AQMA Italia S.p.A) provides a ready-to-use glutathione with high bioavailability and a mixture of a lot of antioxidant compounds that improve the effect of glutathione as primary cellular defender against free radicals produced by ozone therapy. The combined use of antioxidant supplementation and ozone therapy improves tolerance to oxygen-ozone treatment; the timing of administration is important to avoid nullifying the therapeutic effects of ozone.

In parallel with the chemical and biological synergism resulting from the use of antioxidants in combination with oxygen-ozone therapy, it is important to underline that the intervention with nutraceutical formulations that improve sleep and mental well-being represents a further synergistic strategy with ozone therapy. In this case the correlation is not directly deductible, as in the case of antioxidants use, but there is a physiological connection regarding the effects that both, nutraceutical and ozone interventions, have on the nervous system and stress management: they possess a functional synergism. Ozone works on the body at the vascular, inflammatory, and oxidative levels, while the nutraceutical supplement based on Ashwagandha, Lemon Balm, Passionflower, Valerian, Melatonin, group B vitamins and minerals (Ansivor®, AQMA Italia S.p.A), optimizes the nervous system's response and reduces the psycho-emotional impact of pain and of the treated pathology.

Lastly, also topical intervention based on a gel/foam formulation with Cannabis sativa oil enriched in CBD, escin, bromelain, Boswellia extract, glucosamine sulphate, MethylSulfonylMethane (MSM) and methylsalicylate (Cibides lipogel® or Cibides spuma®, AQMA Italia), can support ozone therapy, since both treatments have therapeutic synergy in chronic inflammatory or neuropathic pain, diseases with a strong oxidative component, autoimmune or degenerative diseases. In this case the key role for the therapeutic synergy has proven to be the timing of administration, since ozone induces an oxidative stimulus that the body compensates for with its own defenses and local treatment with lipogel or foam, used after the session, reduces the risk of excessive oxidative stress and supports anti-inflammatory recovery.

The results of this study suggest that the combination of oxygen-ozone therapy and nutraceutical supplementation, administered systemically and topically, can produce a synergistic effect in reducing chronic pain. The anti-inflammatory, antioxidant, and regenerative effects of ozone, combined with the metabolic support of supplements, appear to contribute significantly to clinical improvement. This approach could represent a useful non-pharmacological therapeutic option, especially for patients refractory to conventional treatments. However, the study has some limitations, including the lack of a control group, the relatively small number of patients, and the short follow-up duration. Future randomized, controlled trials will be needed to confirm these preliminary data.

In conclusion, integrated treatment with oxygen-ozone therapy and oral and topical nutraceutical supplementation showed efficacy and good tolerability in the management of chronic musculoskeletal pain, suggesting that new personalized therapeutic models, oriented towards the integration of traditional and complementary medicine, can be exploited for patients suffering from pain.

**Conflicts of Interest:** The authors declare no conflict of interest.

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