

OZONOTHERAPY AS PAIN TREATMENT IN LOWER LIMBS: SYSTEMATIC REVIEW

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Abstract: To evaluate through a systematic review the effectiveness of ozone therapy for the treatment of pain in the lower limbs. **Methods:** To achieve this objective, the methodology adopted involved a systematic search in the ScienceDirect, PubMed and SciELO databases, using a structured combination of specific keywords. Literature review studies and clinical studies relevant to the theme were included. The inclusion criteria involved the selection of studies in English, Portuguese and Spanish that addressed the application of ozone therapy in the treatment of pain in the lower limbs. We excluded articles that had no direct relationship with the theme, as well as case reports, case series, coursework, theses and dissertations. **Conclusion:** Chronic pain in the lower limbs is a prevalent condition, often caused by traumatic injuries, degenerative joint diseases, peripheral neuropathies and/or circulatory disorders. In addition to the physical impact, this condition limits mobility and significantly affects people's quality of life. Conventional treatments, although widely used, often have limited efficacy and potential adverse side effects, driving the search for more effective and safe therapeutic alternatives. Utilizing the oxidative potential of ozone, this therapy is administered in various forms, including topical, subcutaneous, venous and rectal applications.

Keywords: Ozone therapy, oxygen-ozone therapy, acute pain, chronic lower limb pain.

INTRODUCTION

Chronic lower limb pain is a prevalent condition that affects individuals of all ages and

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backgrounds. This pain can have different etiologies, including traumatic injuries, degenerative joint diseases, peripheral neuropathies, circulatory disorders and even genetic factors (SUCUOGLU, 2021). Pain in the lower limbs not only causes physical discomfort, but can also significantly limit patients' mobility and quality of life. Furthermore, it interferes with daily activities and contributes to emotional suffering, creating an urgent need for effective treatments to improve the condition of these individuals (HASSANIEN, 2018).

The complexity of chronic pain demands a multidisciplinary therapeutic approach, various treatments have been explored, from analgesics, opioids and anti-inflammatory medications, to physiotherapeutic and surgical interventions. However, many of these treatments have limited effectiveness and can cause adverse side effects (DRUMOND, 2000). Therefore, there is a constant search for therapeutic alternatives that offer effective pain relief with an acceptable safety profile. In this context, ozone therapy has emerged as a promising option due to its anti-inflammatory, analgesic and antioxidant properties (GARIN, 2008).

The challenges in treating chronic pain are multiple. Variability in patients' response to conventional treatments, the presence of comorbidities, and the chronic nature of pain complicate effective management of this condition. Furthermore, many pharmacological treatments can cause dependence or undesirable side effects, which limits their long-term use. Therefore, the need for alternative treatments that can offer sustainable pain relief without significant adverse effects is evident (SMITH, 2017).

Ozone therapy is a treatment that uses the oxidative potential of ozone, a molecule composed of three oxygen atoms. This therapy involves the administration of a gaseous mixture of oxygen and ozone, which can be applied in a variety of ways, including topically, subcutaneously, intravenously and rectally, depending on the condition. The conversion of medical oxygen into medical ozone ensures that therapeutic ozone is obtained without by-products. This treatment has been widely studied and applied to various health problems, due to its multiple beneficial properties (GARIN, 2008).

The benefits of ozone therapy are broad and include anti-inflammatory, analgesic and



antioxidant actions. Ozone can act as a powerful antiseptic, in addition to improving oxygen delivery to tissues and releasing growth factors, promoting recovery in cases of vascular problems and osteoarticular disorders (DRUMOND, 2000).

The application of ozone therapy in the treatment of chronic pain in the lower limbs is based on its ability to modulate inflammatory processes and improve tissue oxygenation. Preclinical and clinical studies have shown that ozone can relieve pain and improve lower limb function, thanks to its anti-inflammatory and analgesic properties. These effects are achieved by local or systemic administration of ozone, depending on the characteristics of the pain and the patient's condition (BOCCI, 2005).

Although ozone therapy has gained popularity as a therapeutic alternative, scientific evidence on its effectiveness and safety in treating lower limb pain is still limited. The systematic review and meta-analysis proposed in this work aim to gather and critically analyze the available studies on the use of ozone therapy for the treatment of pain in the lower limbs (URITS, 2019 and DALL'OLIO, 2014).

Through this systematic review and meta-analysis, we seek to expand the understanding of ozone therapy as a therapeutic option for pain management. Critically analyzing the available literature, providing a solid basis for clinical decision making and advancing scientific knowledge in this crucial area of clinical practice.

GOAL

To evaluate, through a systematic review, the effectiveness of ozone therapy for the treatment of pain in the lower limbs, identifying the mechanisms of action of ozone therapy in relieving chronic pain and comparing the results with other conventional treatments for chronic pain in the lower limbs.



METHODOLOGY

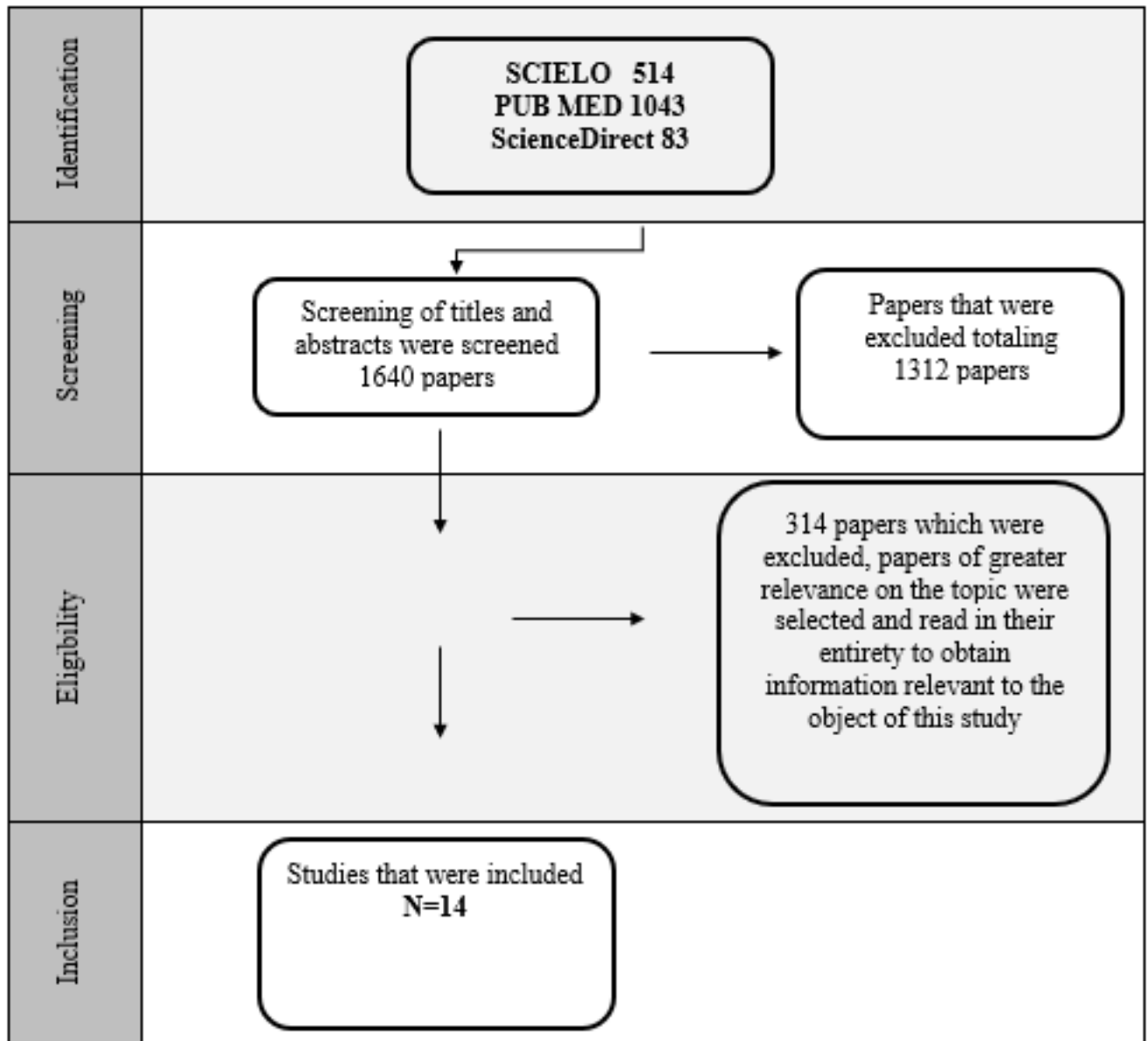
The methodology of this literary review study involved carrying out systematic searches in the PubMed and SciELO databases. To identify relevant and high-quality studies, a structured search strategy was used by combining specific keywords. This approach included the selection of literature review articles and clinical research relevant to the topic investigated. Articles that were not directly related to the topic were excluded, as well as theses and duplicate articles between the databases, to guarantee the relevance and exclusivity of the analyzed data. This procedure ensures that the review covers only the most pertinent and rigorously evaluated evidence available in the scientific literature.

The following were adopted as inclusion criteria for searching for studies: studies that evaluated different treatments for the correction of clinical treatment studies and exclusion criteria, articles from any language other than English, Portuguese and Spanish were not used, articles unrelated to the topic, in addition to reports and case series, course completion works, thesis and dissertations. In the end, after applying the election criteria for the selection of literature, for the development of the study, articles that do not fit the pre-established criteria will be excluded and the selected articles of greatest relevance on the topic will be used.

DATA COLLECTION PROCESS

For the work, research was carried out through scientific articles, where their contents were extracted, such as authorship and year of publication, relevance of the present work and also the type of study such as literature reviews and countries of origin. The evaluation of the data collected in the review articles was carried out through a compilation of the main points relating to the following aspects, using key words.





DISCUSSION

Ozone therapy originated in Germany and the Soviet Union during the First World War, and has since spread throughout Europe, China and America. However, only in Russia, Cuba, Spain and Italy is this technique legal. The scientific literature on its use in pain is still limited. Studies



demonstrate that ozone therapy has promising therapeutic potential (CEDEÑO, 2020).

This technique is based on the application of a mixture of oxygen and ozone, used for therapeutic purposes for many years. Recent studies indicate that the controlled application of ozone can generate oxidative stress capable of correcting imbalances caused by acute or chronic oxidative injuries. This treatment has been shown to increase the activity of antioxidant enzymes, neutralizing the excessive formation of reactive oxygen species, promoting important therapeutic effects (WILSON, GANDHI, SMITH, VATSIA, KHAN- 2017).

The analgesic effect of ozone on pain stands out as an effective therapeutic alternative, it is often compared to the hyperbaric oxygen chamber (HBOT), however, the intra-articular application of ozone is considered more effective, practical and economical. While HBO provides pure oxygen in a pressurized environment, ozone therapy is a gaseous mixture of oxygen and ozone (HERNÁNDEZ, 2012). And it triggers a series of mechanisms that normalize oxygen supply for several days, correcting diseases associated with ischemia, infections and oxidative stress. (VALLONE, 2014)

Ozone reacts with several biological compounds, promoting therapeutic benefits. Its mechanism of action is not yet fully understood, but it includes the inactivation of microorganisms, the stimulation of oxygen metabolism and the activation of the immune system. Thus, ozone activates cellular metabolism, reduces oxidative stress and increases tissue oxygen supply, providing pain relief and improving joint function. (MARQUEZ, 2011).

According to SEYAM et. al, (2018), this technique has been used as an alternative treatment for knee osteoarthritis, aiming to improve patients' symptoms and quality of life, since there is still no cure for this pathology and the applications of ozone They can be performed periarticularly, intraarticularly and subcutaneously, providing a diverse and minimally invasive approach to managing pain and inflammation associated with osteoarthritis.

According to ANZOLIN (2019), in the treatment of osteoarthritis, ozone acts as a bioregulatory agent, releasing factors from endothelial cells and normalizing cellular redox status. Furthermore, O₃ influences the levels of cytokines in the body, ozone reduces the concentration



of TNF- α , a pro-inflammatory cytokine that increases mitochondrial production of reactive oxygen species (ROS) in osteoarthritis. By inhibiting TNF- α , O₃ can interrupt the harmful NF κ B pathway, reducing inflammation. Additionally, ozone increases levels of TGF- β 1, a cytokine crucial for tissue remodeling.

NF κ B, although it is a fundamental regulator of inflammatory responses and cell proliferation, has effects that vary according to the type of cell and can promote cell proliferation or apoptosis. This variability highlights the complexity of the inflammatory response in osteoarthritis and the need for treatments that can effectively modulate these responses. Thus, studies suggest that ozone therapy may be a promising intervention to control inflammation and improve the quality of life of patients with knee osteoarthritis, although more research is needed to fully understand its mechanisms of action and optimize its use (SEYAM et al ., 2018).

The benefits of the technique using oxygen-ozone for treating pain in the lower limbs are diverse. Ozone therapy has been shown to have analgesic properties, helping to reduce pain intensity and significantly improving patients' quality of life, allowing them to resume their daily activities with more comfort. Additionally, ozone has anti-inflammatory effects, reducing inflammation in lower limb tissues, which is especially useful in conditions such as arthritis, where inflammation contributes to joint pain and stiffness. Ozone therapy can also improve blood circulation, promoting wound healing, reducing swelling and relieving the feeling of heaviness and fatigue in the legs. Another benefit is stimulation of the immune system, with ozone strengthening the immune system by increasing the activity of white blood cells and promoting the release of growth factors that stimulate tissue regeneration. It can be mentioned that it also has antimicrobial and antifungal properties, helping to reduce the risk of secondary infections in wounds on the lower limbs. Furthermore, the pain relief provided by ozone therapy can allow patients to reduce the amount of analgesic medications they take regularly, thus minimizing the side effects associated with these medications. Many patients report a rapid improvement in symptoms after treatment with ozone therapy, resulting in a faster recovery and return to normal daily activities (ULUSOY, 2019).



The main indications for ozone therapy for the lower limbs are varied. In cases of arthritis, both osteoarthritis and rheumatoid arthritis can cause chronic pain and inflammation in the joints of the lower limbs. In this case, there is an indication to reduce joint inflammation, relieve pain and improve joint function in these patients. Muscle and joint injuries, such as muscle strains, ligament sprains and joint injuries, can also be treated with ozone therapy, which accelerates healing, reduces pain and restores normal function to the affected limb. In conditions of peripheral neuropathy, such as diabetic neuropathy, nerve compression, and traumatic nerve injuries, ozone therapy improves blood circulation around the nerves, reduces inflammation, and relieves symptoms of neuropathy. In circulatory disorders, such as chronic venous insufficiency and peripheral arterial disease, ozone therapy improves circulation, promotes ulcer healing and reduces associated pain. For patients with chronic pain in the lower limbs, ozone therapy is an effective option for pain management, helping to reduce pain intensity, improve physical function and increase quality of life (ANDRADE, 2019).

As an absolute contraindication, we have Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency: Individuals with G6PD deficiency may be at risk of hemolysis when exposed to ozone, due to the increased production of free radicals. Therefore, ozone therapy is contraindicated in patients with this condition (ULUSOY, 2019 and ANDRADE, 2019).

Among the limitations detected during the development of this systematic review, the small number of published articles available that fit the inclusion and exclusion criteria can be highlighted. Although the selected studies had a good number of participants, none of them were carried out considering specific cases and the Brazilian population.

CONCLUSION

Ozone therapy has demonstrated effectiveness in treating chronic pain in the lower limbs, as evidenced by partial data from this ongoing study for a doctoral thesis. Preliminary results indicate that ozone relieves pain, reduces joint stiffness and improves physical capacity in patients with



traumatic injuries, degenerative joint diseases and peripheral neuropathies. Its anti-inflammatory and analgesic properties, attributed to the antioxidant characteristics of ozone, are used through different routes of administration, such as intra-articular and rectal, allowing personalized adaptation of the treatment. Standardization of application protocols is essential to optimize clinical results, defining ideal concentrations, frequency and duration of treatment. Considering the significant prevalence of pain in the lower limbs, the incorporation of ozone therapy as an accessible therapeutic option in public health is relevant, offering safe and effective alternatives to improve patients' quality of life. However, more research is needed to confirm its long-term effectiveness and establish accurate clinical guidelines. Continuing these investigations is essential to validate the full potential of ozone therapy and its adequate implementation in clinical practice.

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