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REVISÃO

Effects of ozone therapy on joint rehabilitation in patients with osteoarthritis: a systematic review

Efeitos da ozonioterapia na reabilitação articular de pacientes com osteoartrite: uma revisão sistemática

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Abstract

Introduction: Osteoarthritis is a comorbidity of chronic and multifactorial pain, characterized by a degenerative joint process that compromises functionality. Ozone therapy has proven to be a good rehabilitation strategy in view of its regenerative and antioxidant effects. *Objective:* To describe the effects of ozone therapy on tissue recovery, with regard to pain and functionality, impacting the joint rehabilitation of patients with osteoarthritis. *Methods:* Refers to a systematic review guided by the PICO strategy, the search was performed in the Lilacs, Pubmed, and CENTRAL databases, with the descriptors: osteoarthritis, degenerative arthritis, cartilage, damaged cartilage, arthritis, joint, ozone, ozone therapy, ozone therapy, ozone injection, pain, arthralgia, chronic pain, joint pain, mobility, mobility limitation, range of motion and functionality, using the Boolean operators "AND" and "OR", including articles from 2016 to 2021. *Results:* After reading the title and abstract, 40 studies were found, 5 were selected according to the inclusion criteria, which showed that ozone therapy is effective in joint rehabilitation for pain and functionality markers. However, with differences in duration of effects when compared to other therapies, being more effective in the short term. *Conclusion:* Ozone therapy is effective in reducing pain and inflammation, and in

functional improvement, directly impacting the joint rehabilitation of patients with osteoarthritis.

Keywords: ozone; cartilage; articulation; inflammation.

Resumo

Introdução: A osteoartrite é uma comorbidade de dor crônica e multifatorial, caracterizada por um processo articular degenerativo que compromete a funcionalidade. A ozonioterapia tem provado ser uma boa estratégia de reabilitação tendo em conta os seus efeitos regenerativos e antioxidantes. *Objetivo:* Descrever os efeitos da ozonioterapia na recuperação tecidual, no que diz respeito à dor e funcionalidade, impactando na reabilitação articular de pacientes com osteoartrite. *Métodos:* Revisão sistemática orientada pela estratégia PICO; a busca foi realizada nas bases de dados Lilacs, Pubmed e Central, com os descritores: osteoartrite, artrite degenerativa, cartilagem, cartilagem danificada, artrite, articulação, ozônio, terapia de ozônio, ozonioterapia, injeção de ozônio, dor, artralgia, dor crônica, dor articular, mobilidade, limitação de mobilidade, amplitude de movimento e funcionalidade, utilizando os operadores booleanos “AND” e “OR”, incluindo artigos de 2016 a 2021. *Resultados:* Após leitura do título e resumo, foram encontrados 40 estudos, e 5 foram selecionados de acordo com os critérios de inclusão, que mostraram que a ozonioterapia é eficaz na reabilitação articular para marcadores de dor e funcionalidade. Porém, com diferenças na duração dos efeitos quando comparado a outras terapias, sendo mais eficaz em curto prazo. *Conclusão:* A ozonioterapia é eficaz na redução da dor e inflamação, e na melhora funcional, impactando diretamente na reabilitação articular de pacientes com osteoartrite.

Palavras-chave: ozônio; cartilagem; articulação; inflamação.

Introduction

Osteoarthritis (OA) is characterized by a degenerative process of the joint, with morphological changes, especially in cartilage, generating joint incongruence, reducing functionality, impacting the quality of life and mental health of the individual. In this context, ozone therapy has been consolidating its regenerative effectiveness, thus favoring mobility, biomechanics, and joint functionality [1,2].

This pathology is considered chronic and multifactorial, of non-genetic character, not linked to aging and gender, but a higher percentage in women and the elderly stands out. It is the most common cause of disability and affects up to 15% of the population

over 60. According to the United Nations (2004), by the year 2050 this figure will increase to 20%, that is, 130 million people will be affected [3,4].

Osteoarthritis is a chronic pain comorbidity that can affect any joint, however, with greater incidence in hips, knees, hands, feet and spine. Through which, the inflammatory process in the synovial fluid causes deterioration of the cartilage and adjacent structures, such as muscles, tendons, and ligaments, causing bone deformities, pain, edema, stiffness, and loss of function [5].

Ozone therapy promotes the synthesis of antioxidant enzymes, inhibits the action of pro-inflammatory cytokines, and stimulates anabolism. These processes favor angiogenesis and stimulation of cells that are directly linked to the maintenance of the matrix and healing of connective tissue. Thus, enabling an effective action on the symptoms and repair of tissues degenerated by osteoarthritis [6].

The use of ozone as a therapy is still recent; the time of discovery of its pharmacodynamics in human blood is less than half a century. For this reason, the number of studies discussing the effects of ozone therapy on musculoskeletal disorders is, in fact, small. Thus, the present study aims to describe the effects of ozone therapy on tissue recovery, with regard to pain and functionality, impacting the joint rehabilitation of patients with OA.

Methods

Study design

This systematic review was completed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [7].

Eligibility criteria

To perform this systematic review, the PICO strategy was used, whose Population was patients affected by osteoarthritis, having ozone therapy as Intervention. The control group were patients who received placebo treatment, conservative physical therapy, or other invasive interventions. In the endpoints, the search was related to pain and functionality.

Information sources

The search for articles was conducted in the Latin American and Caribbean Literature on Health Sciences (LILACS), Pubmed, and Cochrane Central Register of Systematic Review (CENTRAL) databases. Reference lists of previous systematic reviews and of the clinical trials eligible for this review were also searched. The search for articles ended in September 2021.

Search

The search was based on the previously described PICO strategy and the Boolean operators AND and OR. The keywords were extracted from the Health Sciences Descriptors (Decs), and for the population: osteoarthritis, degenerative arthritis, cartilage, damaged cartilage, arthritis, and joint. As for the intervention: ozone, ozone therapy, ozone therapy, ozone injection. The results were: pain, arthralgia, chronic pain, joint pain, mobility, mobility limitation, range of motion, and functionality. Randomized clinical trials, clinical trials and controlled trials were used as descriptors for the study design.

Study Selection

Randomized clinical trials from the last 5 years, in English, Portuguese and Spanish, involving patients with osteoarthritis were included in this systematic review. To be eligible, the clinical trial had to have assigned patients with osteoarthritis to an ozone therapy treatment group. Studies with adults (18 years and older), regardless of gender, were also included. Ozone therapy refers to the medicinal use of the triatomic oxygen molecule, produced from a medical generator, for the treatment of various conditions. It is possible by several routes of administration, such as intra-articular, periarticular, subcutaneous, rectal, venous, auricular, and vaginal. And as exclusion criteria were listed studies that involved tests on animals and related to the use of drugs.

Data collection process

For the extraction of the selected articles, titles (first step), abstracts (second step), and complete reading (third step) were checked. Then, an exploratory reading of the selected studies was performed, followed by a selective and analytical reading. The data extracted from the articles were summarized in authors, year, title, population, gender, mean age, sample size, type of interventions, number of sessions, O₃ concentration used, diagnostic method, follow-up, and scales used to obtain important information for the research.

Data Items

Two authors independently extracted the data from the published reports using standard data extraction considering: (1) aspects of the study population, such as mean age, gender, number of patients, method of diagnosis; (2) aspects of the intervention performed (sample size, type of intervention, number of sessions, O₃ concentration used); (3) follow-up; (4) variables analyzed; and (5); scales used.

Quality of studies

The methodological quality was evaluated according to the criteria of the PEDro scale, which scores 11 items, namely: 1 - Eligibility criteria, 2 - Random allocation, 3 - Hidden allocation, 4 - Baseline comparison, 5 - Blinded, 6 - Blinded therapists, 7 - Blinded assessors, 8 - Adequate follow-up, 9 - Intention to treat analysis, 10 - Inter-group comparisons, 11 - Point estimates and variability. Items are scored as present (1) or absent (0), generating a maximum sum of 10 points, not counting the first item⁸.

Where possible, PEDro scores were extracted from its own database. When articles were not found in the database, a trained independent reviewer evaluated the article with the PEDro scale. Studies were considered of high quality if they scored 8, and excellent quality if they scored 9 to 10.

Results

Forty articles were excluded after reading the titles and abstracts. Eight articles were selected, three of which succeeded to exclusion because they were related to the use of medications, thus remaining five studies by the inclusion criteria. The flowchart in figure 1 shows the criteria and databases used to select the articles.

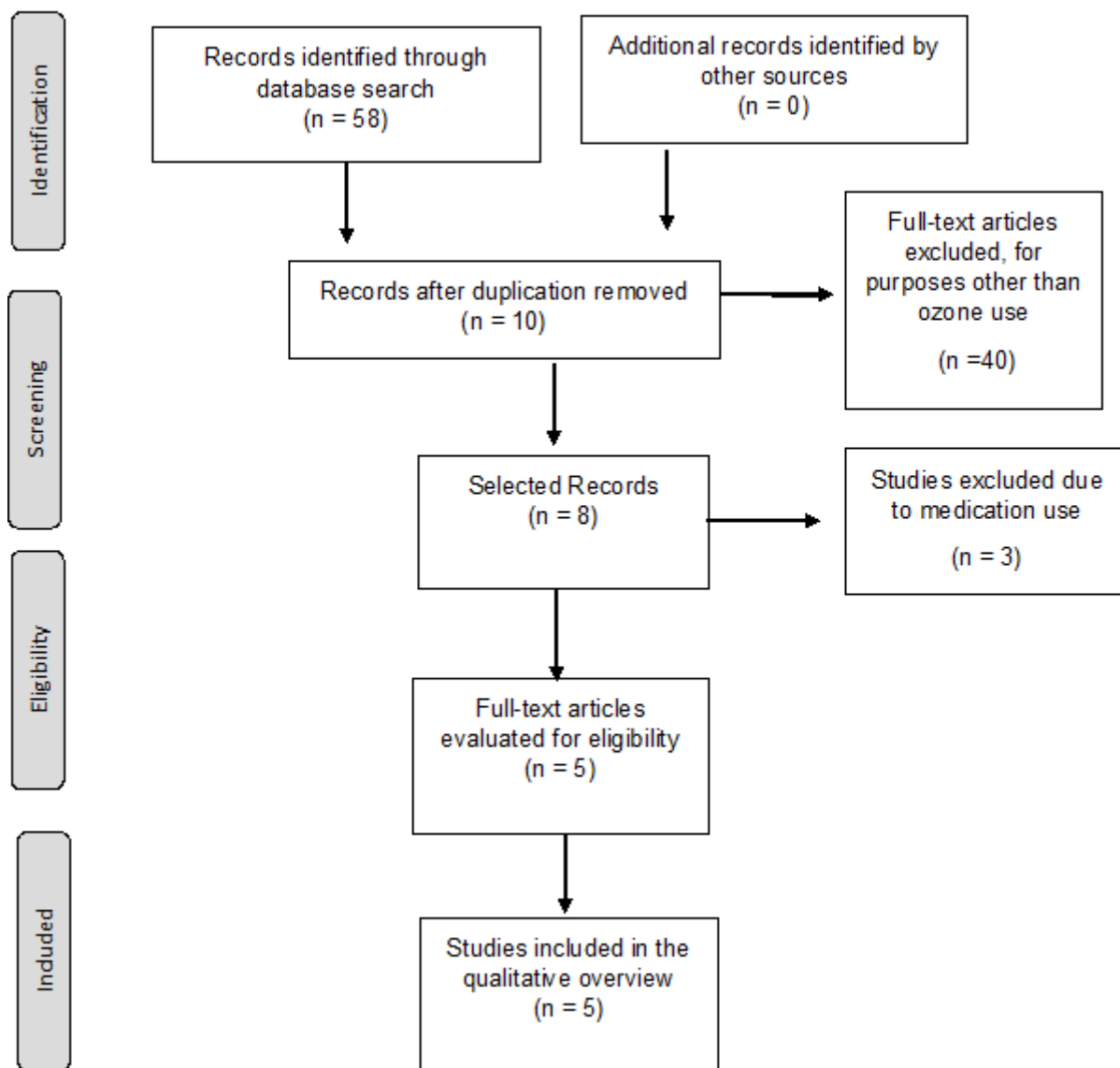


Figure 1 - Flow chart for obtaining randomized clinical trials based on the effects of ozone therapy in patients with osteoarthritis

The methodological quality evaluated by the Pedro scale is shown in Table I. Being that the 5 studies included in this systematic review discuss the effects of ozone therapy on patients with osteoarthritis. Only the study by Sire *et al.* [9] showed good methodological quality while the studies by Raeissadat *et al.* [10,11], Babaei-Ghazani *et al.* [12] and Jesus *et al.* [13] were rated at excellent methodological quality.

Table I - Methodological quality assessment of the studies included in this review, using the Pedro database scale

	Raeissadat <i>et al.</i> [10]	Babaei- Ghazani <i>et al.</i> [12]	Raeissadat <i>et al.</i> [11]	Sire <i>et al.</i> [9]	Jesus <i>et al.</i> [13]
01					
02	✓	✓	✓		✓
03	✓	✓	✓		✓
04	✓	✓	✓		✓
05	✓	✓	✓		✓
06			✓		✓
07	✓	✓	✓		✓
08	✓	✓	✓		✓
09	✓	✓	✓		✓
10	✓	✓	✓		✓
11	✓	✓	✓		✓
Score	9/10	9/10	10/10	8/10	10/10

The summary of the methods used and clinical results are presented in Table II. The scales used to evaluate functionality were the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Lequesne Index (LEQ), Oxford Knee Questionnaire (OKQ), Timed up and go (TUG) and Physical Component Summary (PCS). Those that evaluate pain are the Visual Analog Pain Scale (VAS) and the Geriatric Pain Measurement (GPM).

Table II - General data from the randomized clinical trials included, looking for the effects of ozone therapy in patients with osteoarthritis (see PDF)

Discussion

The results obtained in the studies prove the effectiveness of ozone use for joint rehabilitation, since its efficacy is statistically significant for pain and function markers. However, they show differences in the duration of the effects when compared to other therapies, being more effective in short protocols of up to 6 months.

The authors, Jesus *et al.* [13], Sire *et al.* [9], Raeissadat *et al.* [11], Babaei-Ghazani *et al.* [12] highlight the degeneration factor as the key point in joint destruction, which generates a range of symptoms that have the consequence of disabling the individual, leading to joint incongruity, causing pain, absence of function and decreased quality of life.

In this context, it is believed that ozone therapy is effective in tissue recovery by promoting moderate oxidative stress, being a vehicle for endogenous immune responses, with reduction of pro-inflammatory cytokines and activation of regeneration factors. Thus, it becomes a hope for treatment, besides the low cost, and it can be more accessible to the population, besides making it less costly for the country.

The pain in osteoarthritis is one of the main symptoms experienced by patients affected, since the degeneration is part of a multifactorial inflammatory process, which leads to the destruction of the articular cellular matrix. This triggers a series of problems that accompany the entire process, and increases as the pathology evolves. It is worth pointing out that pain and function are directly related, for the individual with joint pain necessarily has a deficit in function.

Functionality, on the other hand, reflects the biomechanical alignment and joint fluency, which allows stable synergic movements, keeping the individual active throughout life. However, in OA, due to the chronic inflammatory process of the joint structures, especially the cartilage, there is formation of osteophytes and deformities, compromising functionality as a result of incongruity.

Following this reasoning, Raeissadat *et al.* [10] prove the effectiveness and safety of O₃ and HA in pain management and functionality. Although both techniques were effective in relieving symptoms, O₃ was slightly better in the context of pain and stiffness, and HA in the aspect of functionality, but without statistical relevance in the results. Thus, the authors suggest ozone therapy over HA, due to the primary cost-benefit factor.

It is known that ozone therapy is still relatively recent, but it is already used in several painful conditions, as well as in other pathologies, and according to the

suggestion of Raeissadat *et al.* [10] regarding cost-benefit, currently the market values of the two therapies oscillate, with the application of O₃ being around one third of HA. In fact, ozone therapy is a better option, allowing a larger fraction of the population to have access to a promising treatment for OA.

Similarly, Sire *et al.* [9], 6 months after intra-articular application, found that ozone and HA are effective therapies for pain relief. However, they show that in the short term, that is, within one-month, hyaluronic acid is more effective for this symptom. These results may be explained by the absence of a description of the HA concentration in the protocol proposed in this study.

On an opposing side, Raeissadat *et al.* [11] and Jesus *et al.* [13] converge their results to the same reasoning, that O₃ is more effective in the short term, around two months regarding pain, function and stiffness. Possibly, the blockade of pro-inflammatory cytokines has a direct action in reducing pain and consequently improving function.

This condition is explained by the ozone action mechanism, since it has the potential to paralyze the inflammatory process, as well as activating growth factors, in addition to greater vascularization and local O₂ supply. These events trigger an endogenous response from the immune system, which receives the stimulus for the production of antioxidants, which happens quickly, due to the high solubility and short half-life of this gas.

The results found in the studies by Raeissadat *et al.* [11] and Babaei-Ghazani *et al.* [12], support the theory that the effects of ozone may only persist for up to 6 months. For up to three months after applications, Babaei-Ghazani *et al.* [12] elucidated the superiority of ozone in improving pain and functionality when compared to corticosteroid therapy. Raeissadat *et al.* [11], on the other hand, found that the effects of ozone begin to decline after 6 months and at 12 months it is not effective in tissue repair or analgesia.

Throughout the development of the present research, some limitations were experienced, in particular the lack of articles aligned with the search and screening plan. However, they did not affect the results, since the guidelines and methods defined in this systematic review allowed the work to be carried out without generating negative impact, emphasizing in this sense, the high methodological quality of the studies addressed.

Conclusion

Based on the results it is possible to conclude that ozone therapy is a powerful tool for the treatment of osteoarthritis. However, despite being an approved complementary therapy, new studies are still needed, with greater robustness, especially

in the percentage of samples, treatment time, dosages, number and interval of applications, as well as the ideal stage of the pathology for intervention with ozone. Thus, it could become accessible to the entire population in a safe and effective way, aligning the cost-benefit of the treatment with the rehabilitation itself, with regard to the return of joint functionality and, consequently, the individual's physical and emotional well-being.

Conflitos de interesse

Sem conflito de interesse

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Contribuição dos autores

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