

Artigo

TREATMENT OF RHEUMATOID ARTHRITIS WITH OZONE THERAPY:
SYSTEMATIC REVIEW

TRATAMENTO DA ARTRITE REUMATÓIDE COM OZONIOTERAPIA: REVISÃO
SISTEMÁTICA

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ABSTRACT- Introduction: Rheumatoid arthritis (RA) is a chronic and progressive autoimmune disease and is one of the most commonly reported autoimmune diseases. Currently, its treatment is done with the use of medicines. However, new treatment strategies can substantially change the disease's prognosis. A little explored treatment option is Ozone Therapy. **Objective:** To verify the effectiveness of ozone therapy in the treatment of RA through a systematic review. **Methodology:** Articles published in the databases BIREME, PubMed, SCOPUS, Web of Science, EMBASE and Scielo between March 2020 and May 2020 were manually consulted. The inclusion criteria were randomized clinical trials; studies with no publication deadline; studies in any language and patients diagnosed with rheumatoid

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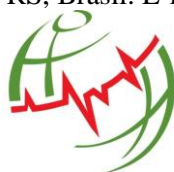
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Artigo

arthritis. Exclusion criteria included studies outside the topic, other types of studies (systematic review, case reports, observational) and patients without a diagnosis for RA. The descriptors used were “Ozone” OR “Ozone Therapy” AND “Arthritis, Rheumatoid”. Results: 77 studies were selected, and only 01 (one) study met the inclusion criteria. **Conclusion:** Considering that only one randomized clinical trial was part of this study, it can be said that the use of ozone therapy was effective in the treatment of RA. In addition, there was an improvement in the individuals clinical status, such as decreased pain and improved functional capacity.

Keywords: Ozone. Ozone therapy. Arthritis, Rheumatoid. Complementary Therapies.

RESUMO- Introdução: A artrite reumatóide (AR) é uma doença autoimune crônica e progressiva e é uma das doenças autoimunes mais comumente relatadas. Atualmente, seu tratamento é feito com o uso de medicamentos. Mas novas estratégias de tratamento podem mudar substancialmente o prognóstico da doença. Uma opção de tratamento pouco explorada é a Ozonioterapia. **Objetivo:** Verificar a efetividade da Ozonioterapia no tratamento da AR através de uma revisão sistemática. **Metodologia:** Foram consultados manualmente artigos publicados nas bases de dados BIREME, PubMed, SCOPUS, Web of Science, EMBASE e Scielo entre março de 2020 a maio de 2020. Os critérios de inclusão foram ensaios clínicos randomizados; estudos sem data limite de publicação; estudos em qualquer idioma e pacientes diagnosticados com AR. Como critérios de exclusão adotou-se estudos fora do tema, outros tipos de estudos (revisão sistemática, relatos de caso, observacionais) e pacientes sem diagnóstico para AR. Os descritores utilizados foram “Ozone” OR “Ozone Therapy” AND “Arthritis, Rheumatoid”. **Resultados:** Foram selecionados 77 estudos, e apenas 01 (um) estudo contemplou os critérios de inclusão. **Conclusão:** Considerando que apenas um ensaio clínico randomizado fez parte desse estudo, pode-se afirmar que a utilização da Ozonioterapia foi eficaz no tratamento da AR. Além disso, houve ainda melhora do estado clínico dos indivíduos, como diminuição da dor e melhora da capacidade funcional.

Palavras-chave: Ozônio. Ozonioterapia. Artrite Reumatoide. Terapias Complementares.



Artigo

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic and progressive autoimmune disease, affecting women more commonly than men (3: 1) (FAVALLI et al., 2019). It is also reported as a disease that results in systemic disorders, which can lead to functional disability because it preferentially affects the synovial membrane, leading to bone and cartilaginous destruction (CONCEIÇÃO et al., 2015).

The onset is usually manifested between 40 and 60 years of age, although the disease can manifest at any age. In addition, RA is highly prevalent and is one of the most frequently reported autoimmune diseases (ADLY et al., 2017).

In RA, magnetic resonance imaging (MRI) allows the detection of all relevant pathologies, such as synovitis, tenosynovitis, bone marrow edema (osteitis), bone erosion and cartilage damage (ØSTERGAAR; BOESEN, 2019). Once diagnosed, treatment varies according to the stage, activity and severity of the disease and aims to improve the quality of life of patients, control the progression of joint injuries, prevent functional loss and decrease pain (SILVA et al., 2018).

Currently, the main drugs used in the treatment of RA are glucocorticoids (GCs) and non-steroidal anti-inflammatory drugs (NSAIDs), used to control pain and inflammation, and the disease-modifying antirheumatic drugs (DMARDs), which are administered as a first-rate medication line for newly diagnosed RA cases (ABBASI et al., 2019).

However, new treatment strategies can substantially change the prognosis of rheumatoid arthritis (RA). Many patients can achieve remission if the disease is recognized early and is treated immediately and continuously; however, some patients do not respond adequately to treatment (BURMESTER; PAPA, 2017).

Therefore, a treatment option little explored is Ozone Therapy (O_2O_3). Ozone Therapy is a gas mixture of about 95% oxygen and no more than 5% ozone (ANAGHA et al., 2016). Ozone is already used worldwide in the treatment of many diseases as it is highly effective against viruses, bacteria and fungi, in addition to having anti-inflammatory action; it acts to increase the local supply of oxygen, promoting local homeostasis and inhibiting bacterial proliferation in numerous diseases, including cancer, rheumatoid arthritis and HIV (RAHIMI-MOVAGHAR, 2012).

Ozone Therapy also has a good immunomodulatory capacity that positively influences RA etiology, justifying the positive results obtained in the treatment of this pathology (FRANZINI; IONITA, 2016). Therefore, the objective of this study was to verify the effectiveness of Ozone Therapy in the treatment of RA through a systematic review.



Artigo

METHODOLOGY

In order to establish the research methods for this systematic review, the prisms of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) were followed, which aimed to answer the following question: *Is Ozone Therapy effective in the treatment of Rheumatoid Arthritis?* To structure it, the components of the acronym PICO (Population, Intervention, Control and Outcome) were used. After that, articles published on the BIREME, PubMed, SCOPUS, Web of Science, EMBASE and Scielo platforms were manually consulted.

The following keywords were used in the PubMed database: ((Ozone therapy) OR ("Ozone" [Mesh] OR "Tropospheric Ozone" OR "Ozone, Tropospheric" OR "Low Level Ozone" OR "Level Ozone, Low" OR "Ozone, Low Level" OR "Ground Level Ozone" OR "Level Ozone, Ground" OR "Ozone, Ground Level ")) AND (" Arthritis, Rheumatoid "[Mesh] OR "Rheumatoid Arthritis "). In the BIREME, SCOPUS, Web of Science, EMBASE and Scielo databases, the descriptors "Ozone Therapy" AND "Arthritis, Rheumatoid" were used. The descriptors were extracted from the DecS (Health Sciences Descriptors). The Boolean operators "AND" and "OR" were used. At PubMed, Mesh (Medical Subject Headings) was used to achieve the maximum number of studies.

The search for studies in these databases was carried out from March 2020 to May 2020. The inclusion criteria for this study were: randomized clinical trials; studies with no publication deadline; studies in any language; and patients diagnosed with Rheumatoid Arthritis. The exclusion criteria were: studies outside the topic, other types of studies (systematic review, case reports, observational) and patients without a diagnosis for RA.

In the first stage, 77 studies were found. Of these, 7 studies at BIREME, 17 studies at PubMed, 15 studies at SCOPUS and 7 studies at Web of Science, 31 studies at EMBASE and no results at Scielo. Of these 77 studies, 40 studies were duplicated, leaving 37 studies to be read (Table 1).



Artigo

Table 1 - Studies found by databases.

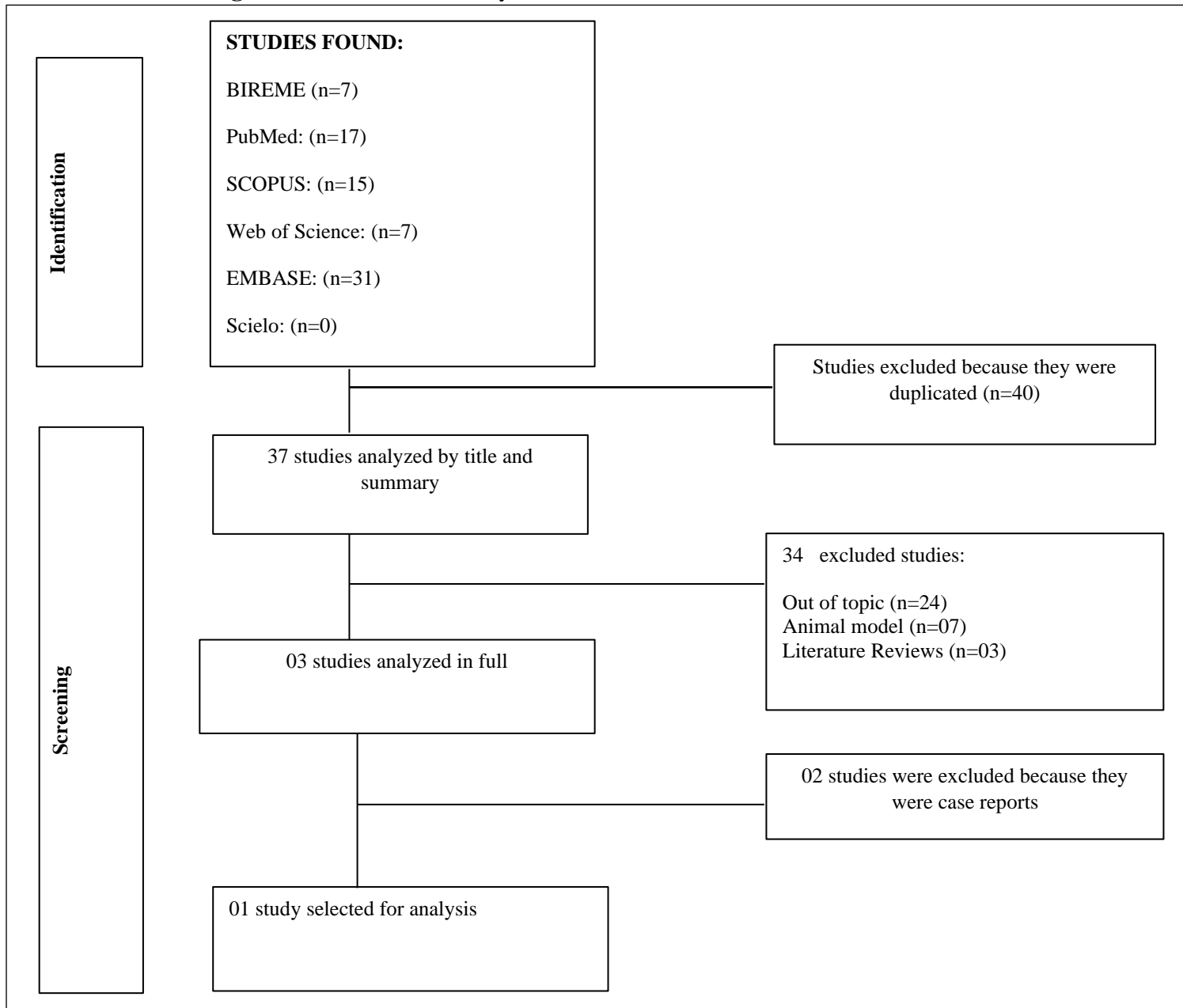
DATABASE	FIRST STEP		
	Total	Repeats	Included
BIREME	7	7	0
PUBMED	17	5	12
SCOPUS	15	8	7
WEB OF SCIENCE	7	0	7
EMBASE	31	20	11
SCIELO	0	0	0
TOTAL	77	40	37

In the second step, two independent reviewers read the titles and abstracts of the studies and a third reviewer checked the information to continue the study. Finally, after reading the 37 articles, only 03 articles had requirements to be read in full, and only one study contemplated the eligibility criteria for this review (Figure 1).



Artigo

Figure 1 - Flowchart of study selection.



Artigo

RESULTS

Only one article met all the necessary criteria and was selected in this study. The article was published in 2016 in the European Journal of Pharmacology (Table 2)

Table 2 - Description of the study.

Title of the Article	Publication Date	Authors	Objective	Groups	Ozone concentration / volume	Parameters evaluated	Conclusions
Medical ozone increases methotrexate clinical response and improves cellular redox balance in patients with rheumatoid arthritis	2016	FERNÁNDEZ et al.	To investigate the medical effects of ozone in patients with RA and treated with methotrexate (MTX) and methotrexate (MTX) + ozone and perform a comparison between groups.	<p>Patients were randomized into two different treatment groups:</p> <p>MTX Group (12.5 mg of intramuscular MTX (IM), once / week every Monday from 9:00 am to 10:00 am Ibuprofen (400 mg, orally), one tablet every 8 h of folic acid (5 mg, orally), One tablet daily from Wednesday to Saturday.</p> <p>MTX + ozone group (same MTX as the previous group + medical ozone, which was generated by an OZOMED ozone generator, Cuba. 20 sessions by rectal insufflation (five times a week from Monday to Friday). 25 mg / L at 40 mg / L of ozone in staggered application and in ascending order were administered as follows: 1st week: 25 mg / L, 100 ml; 2nd week: 30 mg / L, 150 ml; 3rd week: 35 mg / L, 200 ml; 4th week: 40 mg / L in 200 ml.</p>	25 mg / L to 40 mg / L	Anti-CCP antibodies (before and at the end of the study, 21 days); Clinical parameters of DAS28; decrease HAQ-DI and reduction of pain intensity by visual analog scale (VAS).	<p>The MTX + ozone group reduced disease activity, while MTX only showed a tendency to decrease the studied variables. The acute phase reagents displayed a similar image. In the MTX + ozone group, reduced levels of anti-CCP were found, as well as an increase in the antioxidant system and a decrease in oxidative damage, while the MTX group did not change.</p> <p>MTX + ozone increased the clinical response of MTX in patients with RA. No side effects were observed. These results suggest that ozone may increase the effectiveness of MTX, probably because both share common therapeutic targets. Medical ozone treatment is able to complement therapy in the treatment of RA.</p>



Artigo

DISCUSSION

The aim of this study was to find efficacy in the treatment of RA using ozone therapy. To this end, a search for studies was carried out in the main biomedical databases. Only one clinical study in humans has been selected. According to this study, ozone reduces disease activity and the group that received ozone was more effective in treating RA. There was also an improvement in clinical status (pain reduction, DAS28 (Disease Activity Score 28), HAQ-DI (The Health Assessment Questionnaire Disability Index) and acute phase reagent, as well as a reduction in the immune response (anti-CCP) and oxidative stress (FERNÁNDEZ et al., 2016).

According to the Brazilian Association of Ozonotherapy (ABOZ), in order to understand how each professional can use this therapy, it is important to note that Ozone Therapy is part of the National Policy for Integrative and Complementary Practices (PNPIC) of SUS, by Ordinance No. 702 / 2018 from the Ministry of Health. Thus, any professional who can act in these practices can naturally use Ozone Therapy. However, in Brazil, the Federal Council of Medicine (CFM) does not yet recognize the use of this practice. The medical council only allows the gas to be used in scientific research, according to Resolution 196/96 of the National Health Council (CNS, 1996).

At therapeutic doses, ozone can be used as a more effective and safer substitute for standard medications for musculoskeletal disorders, such as RA, lumbar facet, joint syndrome, subacromial bursitis, carpal tunnel syndrome, osteoarthritis, hip bursitis, adhesive shoulder capsulitis and herniated disc (SEYAM et al., 2018). In addition, this therapy can be used in oral diseases, hepatitis and temporomandibular joint disorder (TMD) (ANAGHA et al., 2016).

The parameters evaluated by the selected article were DAS28, HAQ-DI, visual analog scale (EVA) and anti-CCP which will be discussed next. DAS28 have been used to measure RA activity; this method uses 28 joints to count swollen and painful joints, it also allows the optional use of C-Reactive Protein (CRP) as an inflammatory marker instead of ESR (erythrocyte sedimentation rate) and is the most used measure to assess inflammatory activity, both in clinical trials and in daily clinical practice (MEDEIROS et al., 2015). It is important to note that DAS28 was reduced in the MTX + ozone group, while there was no change in the MTX group (FERNÁNDEZ et al., 2016).



Artigo

Another variable used to verify the improvement of the disease was the HAQ-DI, a form that evaluates rheumatoid arthritis. The questionnaire is a result reported by the patient and is usually analyzed by calculating the scores of 20 questions about the ability to perform activities of daily living (ADL). The unique scales vary from 0 (without difficulty) to 3 (unable to do) (POOLE; STEEN, 1991). In the selected study, the results were similar to that of DAS28, MTX + ozone improved the deficiencies of patients with RA (FERNÁNDEZ et al., 2016).

It is important to highlight the use of the visual analog scale (VAS) in the selected study. This is a simple tool for assessing subjective symptoms, such as pain, in which patients report pain intensities through a gradual scale ranging from 0 to 100 mm, where 0 (zero) means no pain and 100 (one hundred) your maximum pain (WEWERS, LOWERS, 1990). Many clinical studies for RA treatment use this scale to assess patients' pain (HETTA et al., 2019; SAID et al., 2019; SHAO KUN et al., 2019). In the study, the group that used MTX + ozone showed a decrease in pain intensity according to this scale, on the other hand, there was no change in pain intensity in the MTX group.

Other important markers in the assessment of RA are rheumatoid factor (RF) and citrate peptide anti cyclic antibodies (anti-CCP) (TAKEUCHI et al., 2017). A randomized double-blind clinical study was conducted to investigate the influences of RF and anti-CCP on the clinical response to a drug called infliximab in RA patients and their relationship to tumor necrosis factor (TNF). The authors concluded that the baseline RF and anti-CCP titers showed significant decreases during treatment with infliximab (TAKEUCHI et al., 2017). These reduced values can be compared with this study in the use of the MTX + ozone group, where anti-CCP levels were reduced. Thus, the results may indicate that the lesions in the cartilage and bone have been reduced (FERNÁNDEZ et al., 2016).

As for ozone doses, in the study selected in this review, the therapeutic doses used were 25 mg / L to 40 mg / L by rectal insufflation, and the results were analyzed after 21 days. In a randomized, placebo-controlled clinical study involving 98 individuals in another rheumatic disease, called knee osteoarthritis (OA), doses of 20 µg / mL intra-articular ozone were used in the first group and in the other, placebo was used, both treated for 8 weeks. This study confirms the effectiveness of ozone in relieving pain, and there was still a functional and quality of life improvement in patients with OA (LOPES JESUS et al., 2017).



Artigo

However, in another study that compared the effectiveness of treatment in three groups of patients with OA ($n = 102$), who received an intra-articular injection of platelet-rich plasma (PRP), hyaluronic acid (HA) or ozone gas (concentration $30 \mu\text{g} / \text{ml}$), it was concluded that in the treatment of mild to moderate knee OA, PRP was more successful than HA and ozone injections (DUYMUS et al., 2016). Another similar study that compared short-term clinical results between intra-articular injection of hyaluronic acid (HA), ozone therapy (O_2O_3) and the combination of both, in patients affected by knee OA, 70 patients were recruited and randomized to receive intra-articular injections of HA ($n = 23$) or O_2O_3 ($n = 23$) or combined ($n = 24$) one per week for 5 consecutive weeks. The combination of treatment with O_2O_3 and HA led to a significantly better result, especially at 2 months of follow-up compared to HA and O_2O_3 when administered separately (GIOMBINI et al., 2016).

A study that recruited 89 patients suffering from knee I-II gonarthrosis aimed to optimize the treatment of these patients with para-articular application of oxygen / ozone therapy and to evaluate the clinical effectiveness of this approach. The group that received oxygen with ozone at doses of $8 \text{ gr} / \text{L}$ for 1 to 6 months showed efficacy during the exacerbation of OA assessed based on the WOMAC index, VAS and Lyshom scale (BARANOVA, 2018).

In humans, clinical research using this therapy in the treatment of RA is scarce, there is more clinical research in OA disease which is another degenerative pathology similar to RA. However, there is some research carried out in rats that showed the effectiveness in reducing $\text{TNF-}\alpha$ activity in the inflammatory process of tissues, which can suppress synovial hyperplasia and RA joint edema (CHEN et al., 2013; VAILLANT et al., 2013; TAŞÇI BOZBAŞ et al., 2017).

The increase in $\text{TNF-}\alpha$ can induce RA symptoms in rats, resulting in multiarticular synovitis and significant proliferation of synovial tissue (CHEN et al., 2013). To verify this statement, a study was carried out to observe the effects of intra-articular ozone injection at different concentrations on the content of tumor necrosis factor ($\text{TNF-}\alpha$), TNF I receptor (TNFR I) and TNFR II in the serum and synovium of rats with RA. Forty-eight Wistar rats were randomized into 8 groups, including 5 ozone groups that received intra-articular injection of 10, 20, 30, 40 or $50 \mu\text{g} / \text{ml}$ of ozone, a blank control group, and an oxygen group. All groups with the exception of the blank control were induced to RA. Ozone treatment was administered once a week for 3 weeks, starting 21 days after shaping. The authors concluded that intra-articular injection of 40



Artigo

μg / ml of ozone can attenuate synovitis in rats with RA, the mechanism of which may involve inhibiting TNF- α and TNFR II activity and increasing TNFR I activity in the synovium (CHEN et al., 2013).

Ozone Therapy was associated with MTX in this clinical trial. MTX is a disease-modifying antirheumatic drug (DMARD) (CHAKR et al., 2017). According to the recommendations of the European League Against Rheumatism (EULAR), MTX should be part of the first RA treatment strategy (SMOLEN et al., 2014). It also reduces signs and symptoms of disease activity, improves functional status and reduces the progression of joint injuries (DA MOTA et al., 2013). That is, according to CHEN et al. (2013), act on the same mechanisms of action as Ozone Therapy, reducing TNF- α .

Finally, it is important to highlight the strengths of this systematic review: sensitive searches were carried out for studies that used Ozone Therapy in the treatment of RA in the main biomedical databases in the world; a qualified and trained team was used to carry out the review. As limitations, this review was unable to make comparisons with other randomized controlled trials using ozone therapy in the same pathology, as only one study was selected. Another weakness is that it cannot be stated what are the ideal doses, routes of administration and dosages in the treatment of RA. According to the studies mentioned, it starts with smaller doses and gradually increases. Another weakness is that the therapy was used with drugs, which does not allow the effects of ozone to be assessed separately. Thus, the need for new randomized clinical trials using Ozone Therapy in the treatment of RA is emphasized.

CONCLUSION

Considering that only one randomized clinical trial was part of this study, it can be said that the use of Ozone Therapy was effective in the treatment of RA. In addition, there was an improvement in the individuals' clinical status, such as decreased pain and improved functional capacity.



Artigo

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