

Ozone Therapy in Knee Osteoarthritis: A Systematic Review

Ozonoterapia na Osteoartrose do Joelho: Revisão Sistemática



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ABSTRACT

Introduction: The aim of this study was to conduct a systematic review in order to examine the effectiveness of ozone therapy on knee osteoarthritis. The objectives were to evaluate the effect over time of ozone therapy in terms of knee pain, functional improvement and radiographic progression.

Material and Methods: A search was carried out on PubMed, Embase, Cochrane Library, Scopus and Web of Science databases to identify randomized and controlled studies focusing on this association. The following descriptors were used in English: ozone therapy, knee osteoarthritis. A descriptive summary and quality assessment was made of all studies included for analysis.

Results: Six randomized and controlled studies were identified. The risk of bias assessment demonstrated that one study was considered as having a moderate risk of bias and the remainder a high risk of bias. No quantitative analysis of the data was performed, as the studies included were not sufficiently homogeneous. The participants in the studies were generally elderly patients with mild to moderate knee osteoarthritis.

Discussion: The variability of ozone therapy and the comparators demonstrates that there is no standardized therapy. Few studies reported adverse effects, and where they occurred, they were mild and associated with the procedure.

Conclusion: Ozone therapy proved effective in the short-term in relation to placebo and when combined with hyaluronic acid, but it was not superior to other current treatments. More randomised and controlled studies are needed to evaluate the risks/benefits of ozone therapy, both in the short term and the medium/long term.

Keywords: Osteoarthritis, Knee; Ozone/therapeutic use

RESUMO

Introdução: O presente estudo teve por objetivo realizar uma revisão sistemática de forma a analisar a eficácia da ozonoterapia na osteoartrose do joelho. Os objetivos visaram avaliar o efeito temporal da ozonoterapia na dor no joelho, na melhoria funcional e na progressão radiográfica.

Material e Métodos: Realizou-se uma pesquisa nas bases de dados PubMed, Embase, Cochrane Library, Scopus e Web of Science a fim de identificar estudos aleatorizados e controlados que tratassem dessa associação. Utilizaram-se os seguintes descritores em língua inglesa: 'ozone therapy', 'knee osteoarthritis'. Realizou-se um resumo descritivo e avaliação de qualidade de todos os estudos incluídos para análise.

Resultados: Identificaram-se seis estudos aleatorizados e controlados relacionados com o objetivo deste trabalho. A avaliação do risco de viés mostrou que um estudo foi considerado como risco moderado de viés e os restantes como risco alto de viés. Não se realizou a análise quantitativa dos dados pois os estudos incluídos não foram suficientemente homogêneos. Os participantes dos estudos eram em geral doentes idosos com osteoartrose do joelho leve a moderada.

Discussão: A variabilidade nas intervenções de ozonoterapia e comparadores, demonstra que não existe uma terapêutica estandardizada. Foram poucos os estudos que relataram os efeitos adversos, e quando aconteceu, estes eram ligeiros e associados ao procedimento.

Conclusão: A ozonoterapia mostrou eficácia a curto prazo, em relação ao placebo e quando combinada com ácido hialurónico, sem ser promissora em relação aos restantes tratamentos vigentes. É importante que novos estudos aleatorizados e controlados avaliem os benefícios/riscos da ozonoterapia tanto a curto como a médio/longo prazo.

Palavras-chave: Osteoartrose do Joelho; Ozono/uso terapêutico

INTRODUCTION

A Knee osteoarthritis is a degenerative joint disease presenting with joint pain, stiffness and progressive functional impairment.¹ It is a challenging health concern, due to its high prevalence, particularly in the elderly.²⁻⁴ The precise pain mechanism is still unclear and knee pain has been related to the joint capsule, synovial membrane, menisci, ligaments and tendons.^{5,6}

Non-surgical treatment refers to a multimodal approach including the use of supplements with glucosamine / chon-

droitin, anti-inflammatory drugs, intra-articular injections, acupuncture, joint protection techniques, physiotherapy, exercise and orthotics, among others.^{7,8} However, knee pain and any of the remaining symptoms are not completely relieved by any of these modalities. No significant advantage with any of these modalities was found in a 2007 study.⁴

Anti-inflammatory and analgesic effects are obtained with ozone therapy and, when used in adequate therapeutic concentrations, may relieve knee pain and improve knee

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articular function with no severe adverse effects.⁹ Ozone has also a bacteriostatic, fungicide and virucide action, therefore with a minimum risk of infection, in addition to the stimulation of oxygen metabolism and activation of the immune system.^{10,11}

Ozone medical benefits have been increasingly well-known and put into practice over the past few years, particularly in musculoskeletal disorders, including low back pain, lumbar disk herniation, periarticular shoulder disorders and knee osteoarthritis.¹²

This study was aimed at a systematic analysis of the controlled and randomised trials on the efficacy of ozone therapy in patients with knee osteoarthritis.

MATERIAL AND METHODS

This systematic review has been registered online with PROSPERO (record number: CRD42017080263), according to the PRISMA declaration guidelines.

Inclusion criteria: Controlled and randomised trials on the assessment of the efficacy of ozone therapy in human knee osteoarthritis. Only studies involving patients 18-years and older with knee osteoarthritis were included in the analysis (P). Studies should include at least one control group of patients treated with placebo, drug or non-drug (C) or other comparison with intra-articular ozone therapy (I). Studies should be written in English or Portuguese and published from 2000 to the end of Oct 2017.

Exclusion criteria: Studies that were only published as an abstract were excluded from the analysis.

Primary and secondary objectives (O): The assessment of pain improvement based on Visual Analogue Scale (VAS) scoring at 1 month, 3 months, 6 months and 12 months was the primary objective of the analysis. Secondary objectives included functional improvement assessment according to the functional Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scoring at 1 month, 3 months, 6 months and 12 months in addition to the assessment of the radiological progression based on the Kellgren-Lawrence grading system scoring at 6 and 12 months. A quantitative analysis would be carried out in the event that studies included in the analysis were sufficiently homogeneous.

Research strategy: A systematic search in PubMed, Embase, Cochrane Library, Scopus and Web of Science was carried out by two researchers by use of the following strategy: 'ozone therapy'/exp AND 'knee osteoarthritis'/exp AND [2000-2017]/py AND [humans]/lim (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/10330/Apendice_001.pdf). A review on all the titles and abstracts was carried out by two researchers in order to remove any duplicate data and to assess for their relevance according to the inclusion and exclusion criteria. In case of ambiguity, the whole text was reviewed and a third researcher would be added to the analysis, in case of disagreement.

Data collection and analysis: Data were independently collected by two reviewers by use of a pre-developed data

extraction table. The baseline characteristics of the studies were extracted in order to obtain descriptive summaries. Data were analysed as regards consistency and discrepancies were discussed until a consensus had been reached. Data quantitative analysis would depend on whether the studies were sufficiently homogeneous regarding the variables that were described by the objectives.

Quality assessment: The methodological quality of each eligible study has been independently assessed by two researchers by use of the Cochrane Risk of Bias tool within the Review Manager 5.3 software in order to assess for the risk of bias of studies in analysis. The following domains were assessed: generation of a randomised sequence (selection bias), concealment of allocation (selection bias), blinding of participants (performance bias), blinding of professionals (performance bias) blinding of outcome assessors (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (outcome bias) and bias from other sources. The risk of bias in each domain was ranked as low (+), high (-) or unclear (?).¹³ A study was only considered at low risk of bias when all the domains were ranked at low risk of bias; when one or two domains were ranked at high or moderate risk, the test was considered at moderate risk of bias; when more than two domains were ranked at high or moderate risk, high risk was considered.¹⁴ A third researcher would be added to the analysis in case of disagreement.

RESULTS

In total, six controlled and randomised studies published between 2015 and 2017 were included in the analysis.^{12,15-19} Selection study details are shown in a flow diagram (Fig. 1).

The characteristics of the studies are shown in a descriptive table (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/10330/Apendice_002.pdf). No quantitative analysis of data was carried out as studies were not sufficiently homogeneous.

Mostly female patients were found, with different ages according to the study; however, mostly patients aged over 50 were included. Knee osteoarthritis was only described as idiopathic by three studies.¹⁵⁻¹⁷ The Kellgren-Lawrence radiological grading system has been used for patient inclusion in all the studies and patients presenting with Kellgren-Lawrence grade II-III were included in four studies^{15-17,19} and patients with Kellgren-Lawrence I-II severity in two studies.^{12,18} Patient's previous therapy has been described in one study,¹⁹ while patients previously on daily analgesics were excluded from two studies^{12,18} and patients with no response to analgesics over the past three months were included in two studies.^{16,17}

Differences between studies regarding therapy regimen have been found, with the number of sessions/interventions ranging between three and twelve, treatment duration between three and eight weeks, ozone dose per injection between 5 and 20 mL, ozone concentration between 15 µg/mL and 40 µg/mL and different routes of administration were described, with the lateral para-patellar approach as

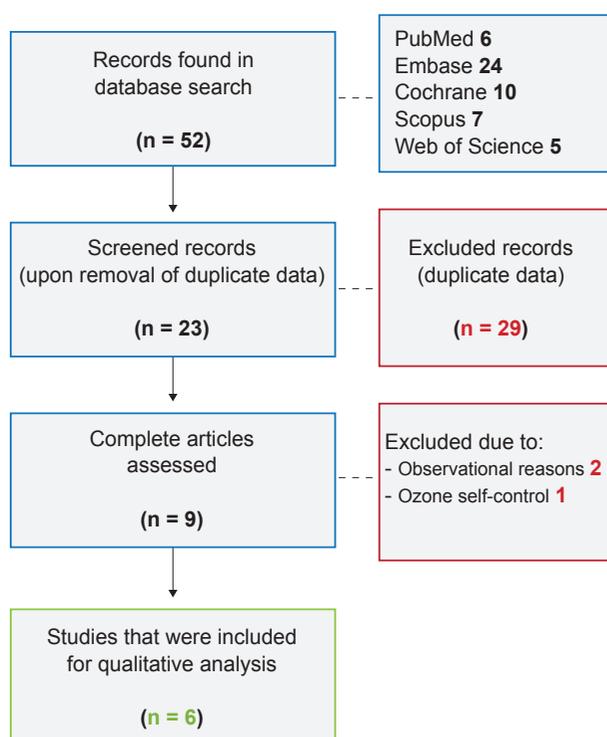


Figure 1 – Study selection flow diagram

predominant.

Different comparisons have been used, including with placebo,¹⁹ hyaluronic acid,^{15,16} platelet-rich plasma,¹⁵ radiofrequency,¹⁷ hypertonic dextrose,¹² celecoxib + glucosamine.¹⁸

The design of the study by Jesus *et al.* was particularly different from the remaining as a neutral comparison has been used, in addition to a concealment of allocation (participants and professionals).

Knee pain assessment was based on the VAS scoring in all the studies. The global WOMAC scoring was used in three studies^{12,15,19} although only two studies^{15,19} have used the functional WOMAC in order to assess functional improvement. The Knee injury and Osteoarthritis Outcome Score (KOOS), which is also a functional evaluation instrument, was used in one study.¹⁶ The radiological progression was not assessed by any of the studies. Different follow-up intervals were found among the different studies, ranging between six weeks¹⁸ and 12 months¹⁵. Short-term durability of clinical outcomes (2-3 months upon the end of treatment)

was analysed by most studies.^{15,16,18,19} The heterogeneity of the assessment intervals based on the VAS scoring is shown in Table 1.

Better outcomes when compared to the placebo group regarding knee pain reduction and improvement in joint function, similar outcomes when compared to the group of patients treated with hypertonic dextrose and with celecoxib + glucosamine and poorer outcomes when compared to the group of patients treated with radiofrequency, hyaluronic acid and platelet-rich plasma were found. In addition, ozone + hyaluronic acid combined therapy was successful in the short term.

As regards comparisons, the same dose and number of sessions as with the ozone therapy was found in the study with hypertonic dextrose, with similar outcomes. In the studies involving the use of radiofrequency, hyaluronic acid and platelet-rich plasma, these were used in less number of sessions as with the ozone therapy and yet better outcomes were found.

Complications were only assessed by two studies^{17,19} and these were mild and particularly associated with the injection site. No reference by any study was made regarding the costs associated with the therapy.

A summary of the assessment of the risk of bias of all the studies that were included in the analysis is shown in Table 2. Only one study was considered at moderate risk of bias,¹⁹ while the remaining were considered at high risk.^{12,15-18} The rationale for the evaluation of each bias domain is shown in Appendix 3 (Appendix 3: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/10330/Apendice_003.pdf).

DISCUSSION

This was a systematic literature review of six recently published controlled and randomised studies, showing an increasing interest in ozone therapy, already with a proved efficacy in other areas.¹²

The fact that predominantly female patients and patients aged over 50 were included in the studies is in line with the prevalence of osteoarthritis in general population.²⁻⁴ The small groups of patients (< 100) involved in most of the studies^{12,16-19} has removed any statistical power to results.

Patients with secondary osteoarthritis with an influence on final outcomes may have been included in studies that did not consider idiopathic osteoarthritis as an inclusion

Table 1 – VAS assessment

VAS scoring (baseline)	1 month	2 months	3 months	4 months	6 months	12 months
Hashemi 2015				x		
Duyms 2016	x		x		x	x
Giombini 2016	5 w		x			
Nabi 2016				4 M 1 w		
Feng 2017	3 w / 6 w					
Jesus 2017	x	x		x		

M: Months; w: Weeks

Table 2 – Evaluation of the risk of bias of all the studies included in the analysis

	Risk of bias	Generation of a randomised sequence	Concealment of allocation	Blinding of participants	Blinding of professionals	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Others sources of bias
Hashemi 2015	High	?	?	?	?	?	?	?	+
Duymus 2016	High	+	?	?	?	?	-	+	+
Giombini 2016	High	+	?	?	?	?	?	?	+
Nabi 2016	High	?	?	?	?	?	+	+	+
Feng 2017	High	+	?	?	?	?	?	?	+
Jesus 2017	Moderate	+	+	+	+	?	+	+	+

criterion, making any outcome comparison even more difficult. Patients with mild to moderate osteoarthritis according to the Kellgren-Lawrence radiological classification were included in all the studies, leaving patients with severe osteoarthritis out of the analysis, with a positive influence on the results.

The lack of homogeneity regarding previous or concomitant therapies was another limitation of the analysis. Some studies have also considered clinical non-response to a previous conservative management as an inclusion criterion, while other studies have excluded patients on daily analgesics.

Different therapy regimens (number of sessions, dose/concentration and treatment duration) in ozone therapy and different comparisons have shown that no standard therapy exists. The study by Jesus *et al.* is worth mentioning due to the longest duration of therapy (eight weeks) and the study by Feng *et al.* in which the highest dose of ozone per intervention has been used. It is reasonable considering that better and long-term outcomes would correspond to longer therapies with higher doses. The fact that it was also a combined treatment should be also taken into consideration. This approach is one of the most frequently used and allows for an easier intra-articular access.

As regards comparisons, the study by Jesus *et al.* should be mentioned as the only study that was based on a neutral comparison with a sham procedure. This was the only double-blinded study considered at a moderate risk of bias, while the remaining studies were considered at high risk, therefore showing their quality.

The outcome comparison has been impaired by the wide variation in study design and the presence of comparisons between different dimensions, namely tablets (celecoxib + glucosamine) vs. intra-articular injections.

A significant reduction in knee pain and rapid onset functional improvement, durable for at least three months has been found with ozone therapy. Retreatment after six months has been recommended by most authors, as symptoms may recur upon this period of time in a small percentage of patients.²⁰

Even though VAS is a validated instrument for the assessment of knee pain, which is a subjective parameter that

may become influenced by other factors, namely sensitive, emotional and cultural factors. The use of other scales, namely the WOMAC, is worth mentioning as it allows for the assessment of functionality apart from pain and stiffness, enhancing the quality of studies that used this instrument.

The inhibition of the high rate of nitric oxide (responsible for apoptosis), inhibition of pro-inflammatory cytokines and improvement in revascularisation were the major mechanisms of action underlying ozone therapy.²¹ The study by Calunga *et al.* has shown that oxidative stress (proved by spectrophotometry) and inflammation (proved by ultrasound imaging) are reduced. The oxidative stress produces the destruction of the cartilage by direct collagen breakdown and by activation of matrix metalloproteinase and, in addition, these are molecules of intracellular signalling amplifying the inflammatory response.²² Therefore, the higher efficacy of the combined therapy with ozone and hyaluronic acid that was found in the study by Giombini *et al.* may have been based on the synergy between both mechanisms of action.

Even though few studies have described adverse effects, these are usually mild and short-term. However, it is worth mentioning that ozone has been used as a mutagenic agent in animal models and cases of de-regulation of the cell cycle related to superoxide radicals have been described.²³ Therefore, the presence of severe adverse effects in the medium and long-term is still unclear.

CONCLUSION

Ozone therapy in patients with knee osteoarthritis has shown its efficacy in the short-term, when compared to placebo and when combined with hyaluronic acid, even though no better outcomes were found when compared to the current treatments (according to VAS and/or WOMAC scoring). There are currently no convincing evidences in favour of a positive risk-benefit ratio of ozone therapy in patients with knee osteoarthritis. Therefore, the effect of ozone should be studied with controlled, randomised, double-blinded, comprehensive and homogeneous trials, using adequate comparisons and always ensuring the presence of patients with similar baseline clinical status in both groups. Homogeneity regarding the outcomes is very relevant and should

be ensured with the use of validated scales. Despite the high subjectivity of the currently validated scales, the use of VAS scoring in knee pain and the WOMAC scale should be ensured. The structural damage and progression of knee osteoarthritis with X-ray or MRI imaging is also crucial, in addition to patient follow-up in the short as in the medium/long-term as well as the assessment of adverse effects and costs.

HUMAN AND ANIMAL PROTECTION

The authors declare that the followed procedures were according to regulations established by the Ethics and Clinical Research Committee and according to the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

CONFLICTS OF INTEREST

The authors declare that there were no conflicts of interest in writing this manuscript.

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