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REVIEW ARTICLE

Effectiveness of ozone therapy compared to other therapies for low back pain: a systematic review with meta-analysis of randomized clinical trials

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KEYWORDS
Low back pain;
Ozone;
Effectiveness of treatment;
Quality of life

Abstract
Background and objectives: Low back pain is a prevalent disease in the adult population, whose quality of life is considerably affected. In order to solve this problem, several therapies have been developed, of which ozone therapy is an example. Our objective in this study was to determine the effectiveness of ozone therapy for lumbar pain relief in adult patients compared to other therapies (steroid and placebo).
Method: We used randomized clinical trials to compare the effectiveness of ozone and other therapies for lumbar pain relief in adults (Prospero: CRD42018090807). Two independent reviewers searched the Medline (1966–April/2018), Scopus (2011–May/2018), Lilacs (1982–May/2018), and EMBASE (1974–March/2018) databases. We use the terms ozone and pain as descriptors. The primary variable was pain relief and the secondary ones were complication, degree of satisfaction, quality of life and recurrence of pain.
Results: Of the 779 identified articles, six selected clinical trials show that ozone therapy is more effective for lumbar pain relief; however, they were mostly classified as having a high or uncertain risk of bias (Cochrane Handbook). The meta-analysis regarding the effectiveness

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of pain relief did not show a significant difference between groups in the three-month period (RR = 1.98, 95% CI: 0.46–8.42, $p = 0.36$; 366 participants). It also showed greater effectiveness of the ozone therapy at six months compared to other therapies (steroid and placebo) (RR = 2.2, 95% CI: 1.87–2.60, $p < 0.00001$; 717 participants).
Conclusions: The systematic review has shown that ozone therapy used for six months for lumbar pain relief is more effective than other therapies; however, this result is not definitive as data from studies with moderate to high risk of bias were used.

PALAVRAS-CHAVE
Dor lombar;
Ozônio;
Efetividade do tratamento;
Qualidade de vida

Efetividade da ozonioterapia comparada a outras terapias para dor lombar: revisão sistemática com metanálise de ensaios clínicos randomizados

Resumo
Justificativa e objetivos: A lombalgia é uma enfermidade prevalente na população adulta, que tem sua qualidade de vida afetada consideravelmente. Com intuito de resolver este problema, desenvolveram-se várias terapias. Um exemplo é a ozonioterapia. Objetivamos neste estudo determinar a efetividade da ozonioterapia para alívio da dor lombar em pacientes adultos, quando comparada a outras terapias (esteroide e placebo).
Método: Usamos de ensaios clínicos randomizados para comparar a efetividade do ozônio e de outras terapias para o alívio da dor lombar em adultos (Prospero: CRD42018090807). Dois revisores independentes analisaram as bases Medline (1966–Abril/2018), Scopus (2011–Maio/2018), Lilacs (1982–Maio/2018) e EMBASE (1974–Março/2018). Como descritores, usamos termos *ozone* e *pain*. Temos como variável primária o alívio da dor e como variáveis secundárias: complicação, grau de satisfação, qualidade de vida e recorrência da dor.
Resultados: Os seis ensaios clínicos selecionados, de 779 artigos identificados, mostram que o grupo do ozônio é mais efetivo para o alívio da dor lombar, porém, foram classificados em sua maioria com alto ou incerto risco de viés (Handbook Cochrane). A metanálise referente à efetividade no alívio da dor não apresentou diferença significante entre os grupos no período de três meses (RR = 1,98; 95% IC: 0,46–8,42; $p = 0,36$; 366 participantes). Também denotou maior efetividade em seis meses do grupo ozônio em relação a outras terapias (esteroide e placebo) (RR = 2,2; 95% IC: 1,87–2,60; $p < 0,00001$; 717 participantes).
Conclusões: A revisão sistemática demonstrou que ozonioterapia usada por seis meses para alívio da dor lombar é mais efetiva do que outras terapias. Entretanto, esse resultado não é definitivo, visto que foram usados dados de estudos com moderado a alto risco de viés.

Introduction

Low back pain is a common condition worldwide, particularly among adults aged 40–80 years, with an estimated prevalence of 11.9%.[1] In Brazil, there is a great heterogeneity of studies showing an annual prevalence of 50% in adults.[2] Its relevance is such that several tools have been developed to measure how low back pain affects people's quality of life. These tools include the Backill Questionnaire and the Oswestry Disability Index.[3]

Low back pain has various forms of treatment, ranging from the most conservative, such as exercise,[4] to the most invasive, such as the need for a surgical procedure.[5] The most common form of treatment is pharmacological, with the use of acetaminophen, dipyrone, opioid, nonsteroidal anti-inflammatory drugs, antidepressants, muscle relaxants, and corticosteroids.[6]

Other therapeutic forms have been developed, such as steroid injection into the lumbar region either by transforaminal or interlaminar approach to the epidural space.[7] Similarly oxygen-ozone mixture has been used as an optional or complementary method for low back pain relief.[8]

According to Bocci et al.,[8] ozone therapy has become a rewarding procedure particularly when compared to surgery. Its benefits range from inhibition of inflammation and correction of ischemia and venous stasis to reflex induction of endorphin release, besides promoting an antinociceptive analgesic mechanism.[8]

The Brazilian Federal Council of Medicine (Conselho Federal de Medicina – CFM) established in the resolution

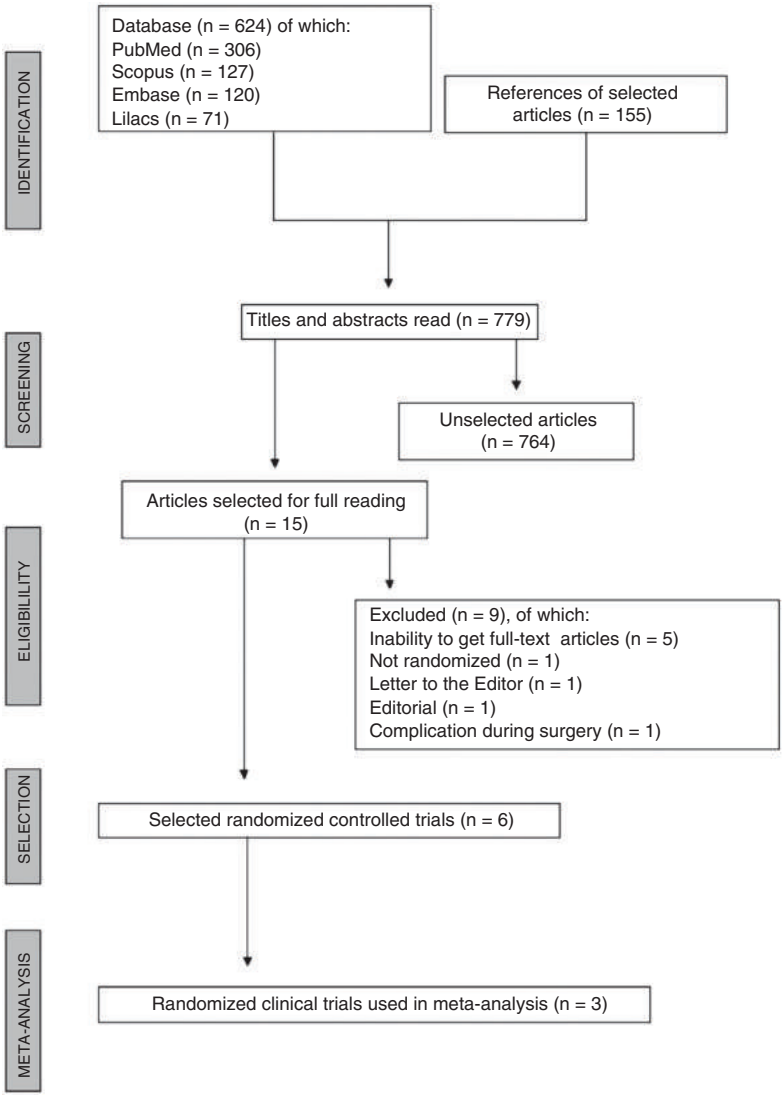

Figure 1 Flowchart summarizing the selection process for original articles.

2181/2018 that ozone therapy is an experimental procedure and can only be used in clinical experimentation with protocols from Research Ethics Committees (Comitês de Ética em Pesquisa – CEP/Conep).[9] The Brazilian Association of Ozone Therapy has presented CFM with recent evidence demonstrating that Ozone Therapy is the best among the existing techniques for treating low back pain and herniated disc.[10]

The CFM's refusal did not prevent the Brazilian Senate from approving the bill 9.001/2017, which authorizes the prescription of ozone therapy throughout the Brazilian territory. At present (May 18th 2019), the bill is pending before the House of Representatives, awaiting the rapporteur's opinion in the Social, Health and Family Affairs Committee (Comissão de Seguridade Social e Família- CSSF).[11]

Controversy over whether or not ozone is used as adjuvant therapy remains. Thus, it is relevant to answer how effective is the use of percutaneous ozone injection in low back pain management.

Based on that, this systematic review aimed to determine the effectiveness of ozone therapy compared to other therapeutic forms for low back pain relief in adult patients.

Method

Protocol

A protocol was developed a priori and registered at the Prospero – International Prospective Register of Systematic Review (http://www.crd.york.ac.uk/PROSPERO/displayrecord.php? ID = CRD42018090807) at York University on March 14, 2018, registration no. CRD42018090807. The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (Prisma-P) 2015 statement was used as a reference to report the data from this systematic review with meta-analysis.[12]

Eligibility criteria

Participants: We included studies with patients over 18 years old, male or female, diagnosed with low back pain in hospitals or clinics for pain management.

We evaluated randomized clinical trials and excluded duplicate articles and those without full description of the data.

Regarding types of interventions, the studies contained two groups of participants, one treated with percutaneous ozone therapy for low back pain and the other treated with another type of low back pain therapy, such as steroids and placebo.

Studies identification

The databases used were:

1) Medline (Medical Analysis and Retrieval System Online) via Pubmed (from 1966 to April 2018) using the search strategy (ozone [MeSH Terms] OR ozone [Text Word]) AND (pain [MeSH Terms] OR pain [Text Word]);
2) Embase (Excerpta Medica database) via Elsevier using the search strategy (low back pain/exp OR acute low back, low pain OR back pain OR chronic low back pain OR loin pain OR low backache OR low backpain OR low backpain OR low back pain lower back pain OR lumbago OR lumbal pain OR lumbal syndrome OR lumbalgesia OR lumbalgia OR lumbar pain OR lumbar spine syndrome OR lumbar syndrome OR lumbodynia OR lumbosacral pain OR lumbosacral root syndrome OR lumbosacroiliac strain OR pain, low back OR pain, lumbosacral OR strain, lumbosacroiliac OR backache/exp OR back ache OR back pain OR back pain syndrome OR backache OR backpain OR dorsalgia OR pain, back) AND (ozone therapy/exp OR ozone therapy) (from 1974 to March 2018);
3) Lilacs (Latin-American and Caribbean Health Sciences Literature) available at Virtual Library of Health-VHL (1982 to May 2018) using the search strategy (tw:((tw: (ozone)) OR (tw: (ozônio) OR (tw:(ozono) AND (tw:((tw: (dor lombar)) OR (tw:(low back pain)) OR (tw:(dolor de espalda); and
4) *Scopus Preview* (from 2011 to May 2018) via Elsevier using the search strategy (Title-abs-key (ozone) AND Title-abs-key (low back pain).
5) In addition, the references of the included articles and previous systematic reviews on this subject were scanned, without restriction of language, date or document format.

Studies selection

Two independent investigators (RRA and FBT) reviewed the titles and abstracts of the retrieved articles. The texts of the initially selected studies were fully read to investigate whether they met the inclusion criteria and selected variables. We contacted the authors of studies not fully available to obtain missing data. Selection disagreements were solved at consensus meetings among reviewers.

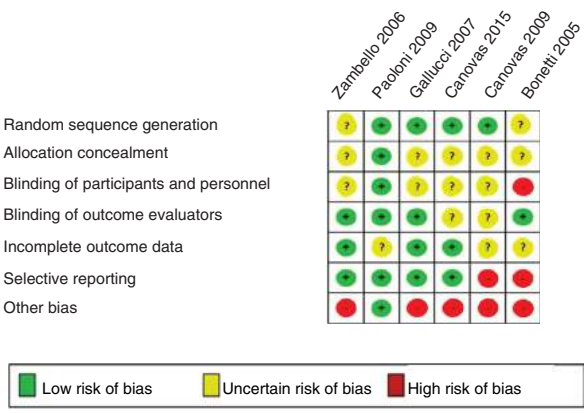

Figure 2 Risk of bias summary.

Bias risk assessment

A Cochrane Collaboration tool was used to assess risk of bias in randomized controlled trials.[13] This tool is based on seven domains: (1) Random sequence generation; (2) Allocation concealment; (3) Blinding of participants and personnel; (4) Blinding of outcome evaluators; (5) Incomplete outcome data; (6) Selective reporting; (7) Other bias.

Each domain was independently evaluated in all articles by two authors (RRA and FBT), the differences were resolved in a consensus meeting. The domains evaluated were classified as: (1) High risk of bias; (2) Low risk of bias; (3) Uncertain risk of bias.

Variables

The primary variable was pain relief, considering the effect and time of symptom follow-up in the studies. Relief was determined as total absence of pain reported by patients or by a score lower than 1 on the Visual Analogue Scale (VAS).

Secondary variables were procedure-related complications, degree of satisfaction, quality of life, and pain recurrence. Complications were defined as syncope, hematoma, headache, and any other condition considered by the authors of the included studies. Satisfaction was defined as the patient's reaction to the treatment received.[14] Quality of life was defined as an aspect of life characterized by physical or mental well-being.[13] Pain recurrence was defined as symptom recurrence after complete relief.

Statistical analysis

Dichotomous variables were analyzed with Relative Risk (RR) and 95% Confidence Interval (CI) using a Random Effects Model. If the effect was absent, we calculated the Risk Difference (RD) with 95% CI and used Random Effects Model. For continuous variables, mean and standard deviation were used to generate Mean Difference (MD) with 95% CI and Random Effects Model.

RevMan 5.3 (Cochrane Collaboration) was used for meta-analysis, and the level of statistical heterogeneity was calculated using chi-square tests, quantified by the Higgins

(I^2) test with a *p*-value <0.10 or <10%, and values of $I^2 > 50\%$ were considered substantial.

Sensitivity analysis

In the presence of statistical heterogeneity ($I^2 > 50\%$), a sensitivity analysis was performed with the removal of articles that might favor the emergence of this heterogeneity. This method of removing articles is not applicable when only two studies are involved in the analysis.

Results

Studies selection

With the search strategies for each database, we found 624 articles whose titles and abstracts were read to assess those with potential to answer the question of our review, as shown in the flowchart of Fig. 1.

Thus, we identified 15 articles for full-text reading. Of these, only six[15–20] remained for the final analysis. Of the nine excluded articles, five[21–25] were not retrieved in full even after attempting to contact their authors; one[26] was not a randomized clinical trial; one[27] was a letter to the editor; one[28] was an editorial; and one[29] centered on complications during surgical procedure.

The 155 references of the six selected articles were analyzed, but no new studies of interest for this review were identified.

Studies evaluation

The risk of study bias was assessed as: high risk of bias, low risk of bias, and uncertain risk of bias, as shown in Fig. 2.

1 *Random sequence generation*: Of the six selected articles, four were considered at low risk of bias for using a computer or computer system[16–18] or a random number table.[20] Two were considered at an uncertain risk of bias for not reporting how they were randomized.[15,19]
2 *Allocation concealment*: Of the six selected articles, only one was considered at low risk of bias because, in addition to having an allocation center, it also used syringes with an opaque, waterproof seal.[16] And five were considered at an uncertain risk of bias, as they did not report enough information to define confidentiality.[17–20]
3 *Blinding of participants and personnel*: Only one study was considered at low risk of bias, as it reports that participants were informed of the possibility of being allocated to the placebo group without their knowledge.[16] One was considered at high risk of bias, as it implies that patients knew which group they belonged to.[15] And four studies were considered at an uncertain risk of bias, as the authors did not make clear the blindness of both participants and personnel.[17–20]
4 *Blindness of outcome evaluators*: Four studies were considered at low risk of bias, as the authors made it clear that the evaluators were blind to the type of treatment assigned.[15,16,19,20] While two studies were considered at an uncertain risk of bias because the authors did not report who were responsible for the outcome assessment.[17,18]
5 *Incomplete outcome data*: Three studies were considered at low risk of bias, as there were no losses to follow-up among participants.[17,19,20] While three studies were considered at an uncertain risk of bias: one for not reporting how many subjects completed follow-up[18]; one for showing mismatch between table and text, which may or may not be a typographical error[15]; and one for showing mismatch between text and table regarding the number of losses, but the losses were justified.[16]
6 *Selective reporting*: Four studies were considered at low risk of bias, as they presented in the results all the proposed variables.[16,17,19,20] While two were considered at high risk of bias: one for presenting data in the results that were not proposed in the variables, but only addressed as inclusion criteria[18]: and one for not presenting data in the results regarding some variables proposed.[15]
7 *Other bias*: Only one study was considered at low risk of bias and the only one to satisfactorily describe the statistical analysis, including sample size calculation.[16] The other five studies reported the statistical tests used, but did not justify the number of participants in each study.[15,17–20]

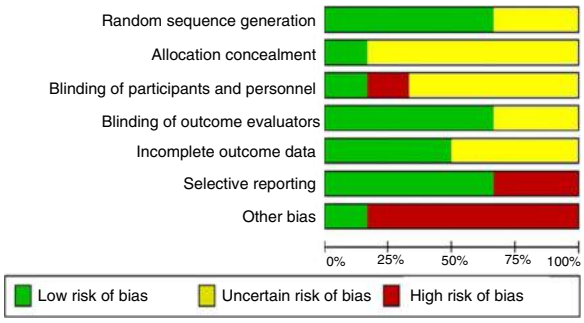

Figure 3 Bias risk graphic.

Variables

Table 1 provides a summary of group characteristics, doses, number of participants, variables, and considerations on randomized clinical trials.[15–20]

Pain relief was the only variable that could undergo meta-analysis. It was not possible to perform a meta-analysis of the following variables: quality of life, pain recurrence, degree of satisfaction, and complications (Figs. 3 and 4).

Five studies used the pain relief variable, three of them as complete pain relief[15,16,19] and two used the visual analogue pain scale.[17,18] Meta-analysis was only possible at three months, which was performed by two studies.[15,16] There was no statistically significant difference between groups using ozone and other therapies (RR = 1.98; 95% CI: 0.46–8.42; $p = 0.36$; 366 participants); and at six months using it, three studies[15,16,19] reported that ozone therapy was statistically superior regarding benefit compared to other therapies (RR = 2.2; 95% CI: 1.87–2.60; $p < 0.00001$; 717 participants).

The variable 'pain recurrence' was not addressed by any of the selected randomized controlled trials.

Table 1 Systematization of randomized controlled trials and their contributions to meta-analysis.

Study year	Groups	N	Dose	Variables	Considerations
Bonetti 2005	Ozone Depomedrol	156 151	3 mL (20 g.mL^{-1}) 2 mL (80 mg)	Pain Relief: Ozone (117/156 with full relief) > Depomedrol (50/156 with full relief) at 6 months.	Patient characteristics: acute or chronic low back pain and sciatica lasting from one to 20 months.
Zambello 2006	Ozone Kenacort	180 171	5 mL (10-20 μg.mL^{-1} 80 mg	Pain Relief: Ozone (72.7% of patients had total pain relief) > Kenacort (45% of patients had total pain relief) – 3 weeks (p < 0.05); Ozone (70% of patients had total pain relief) > Kenacort (31.5% of patients had total pain relief) at 6 months (p < 0.05).	All participants had low back pain with sciatic nerve irradiation over the past 180 days and were unresponsive to tramadol, NSAIDs, steroids, and muscle relaxants.
Gallucci 2007	Kenacort Ozone + Kenacort Kenacort	171 82 77	80 mg 5-7 mL (28 g.mL^{-1}) +2 mL (40 mg.mL^{-1}) 2 mL	Quality of life: ozone (74% of patients had an ODI greater than 20) > Kenacort (47% of patients had an ODI greater than 20) – 6 months (p < 0.01). Complications: There were no complications.	All patients complained of pain for at least eight weeks and had poor or no response to conservative treatment with psychotherapy and/or NSAIDs and/or intramuscular steroid. Oswestry Disability Index (ODI) was used to assess quality of life.
Canovas 2009	Ozone Rf Rf + ozone	10 10 10	5-15 mL (27 g.mL^{-1}) 40 V; 120 s 5-15 mL (27 g.mL^{-1}) + 40 V; 120 s	Analgesic efficacy: ozone + Rf (90% showed an improvement of 6.9 points in VAS) > ozone (80% showed an improvement of 6.1 points in VAS) > Rf (80% showed improvement of 1.4 points in VAS) at 6 months (p < 0.05). Complications: There were no complications.	Patients had symptoms of severe low back pain with VAS score > 6, lasting longer than 3 months and resistance to conservative treatment (oral medications and epidural drugs). Analgesic efficacy was rated best on the Visual Analogue Scale (VAS).

Table 1 (*Continued*)

Study year	Groups	N	Dose	Variables	Considerations
Paoloni 2009	Ozone Placebo	36 24	20 mL (25 g.mL^{-1}) False needle	Pain Relief: Ozone (61% of patients had total pain relief) > Placebo (33% of patients had total pain relief) at 6 months ($p < 0.01$). Quality of life: Ozone (Average difference in Backill questionnaire: +13) > Placebo (Average difference in Backill questionnaire: +5.6) – Not significant. Complications: There were no complications.	Patients had acute low back pain with or without irradiation to one leg for 10 days and no pain episodes in the last 3 months. Backill Questionnaire was used to assess quality of life.
Canovas 2015	Ozone Rf Rf + Ozone	17 17 17	3-8 mL (30%) 2 Hz; 10 ms; 60 V 3-8 mL (30%) +2 Hz; 10 ms; 60	Analgesic efficacy: Rf + ozone (patients showed 4.1 point improvement in VAS) > ozone (patients showed 1.9 point improvement in VAS) ($p = 0.02$) Rf + ozone > Rf (patients showed improvement of 1.7 in VAS point) ($p = 0.009$) at 12 months; Satisfaction: Rf + ozone (88.2% scored 1–2 points) > Rf (70.5% scored 1–2 points) > Ozone (65.6% scored 1–2 points) – ($p < 0.01$) Complications: There were no complications.	Patients had lumbosacral pain radiating to the buttock, unilateral or bilateral, non-rooted with VAS score between 7–9. It is presented as a prospective observational study, but describes the entire intervention. Degree of satisfaction of 1–7 points on their own scale; the lower the value, the greater the degree of satisfaction.

NSAIDs, nonsteroidal anti-inflammatory drugs; N, number of participants; Rf, radiofrequency; ODI, oswestry disability index; VAS, visual analogue scale.

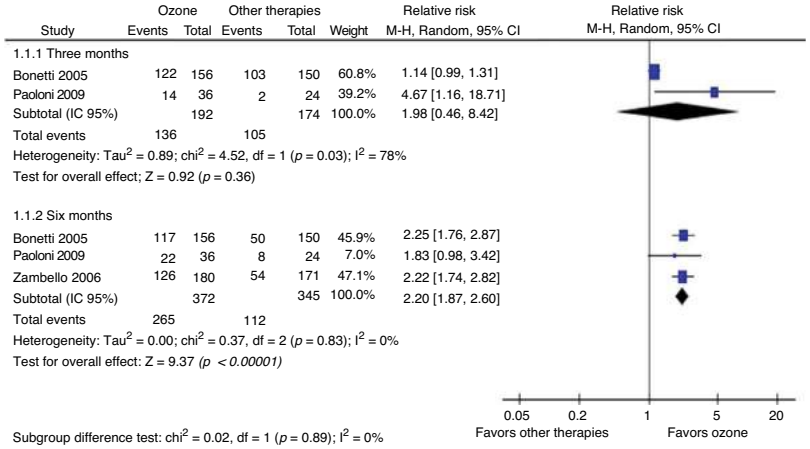

Figure 4 Meta-analysis including three studies of the pain relief variable.

Only one study considered 'degree of satisfaction' as a variable.[17]

Only two studies considered 'quality of life' as a variable,[16,20] but adopted different measures.

Four studies considered procedure-related complications as a vaiable.[16–18,20]

Sensitivity analysis

For the pain relieve variable, it was only possible to perform a meta-analysis with the follow-up times of three[15,16] and six months.[15,16,19]

During the three-month follow-up, there was statistical heterogeneity in two studies[15,16] ($Tau^2 = 0.89$; $chi^2 = 4.52$; $df = 1$, $p = 0.03$; $I^2 = 78\%$). However, withdrawing one of the studies in order to assess sensitivity precludes meta-analysis. Thus, sensitivity analysis was not necessary.

During the six-month follow-up, there was no statistical heterogeneity between three studies[15,16,19] ($Tau^2 = 0.00$; $chi^2 = 0.37$; $df = 2$, $p = 0.83$; $I^2 = 0\%$).

Discussion

The meta-analysis showed that pain relief with ozone therapy at six-month follow-up was superior to other forms of therapy ($p < 0.00001$), with no difference in effectiveness at three-month follow-up ($p = 0.36$). This indicates that, to date, there is no support in the analyzed evidence for the common use of this drug.

A systematic review with meta-analysis[30] showed favorable results for ozone therapy ($p < 00001$), but the authors included the study by Gallucci et al.,[20] which does not report pain relief but quality of life using the Oswestry Disability Questionnaire, along with other studies[15,16,19] that used pain relief as a good response.

All analyzed studies[15–20] appeared to be favorable to the use of ozone therapy for low back pain treatment, but with the Cochrane Collaboration's tool to assess risk of bias.[13] Most studies[15–20] showed a high or uncertain risk of bias, and allocation concealment and blinding of participants and personnel were the highest risk domains, as it was not clear whether they were performed or how.

The studies by Zambello et al. (2006),[19] Canovas et al. (2009),[18] Canovas et al. (2015),[17] Bonetti et al. (2005),[15] and Gallucci et al. (2007)[20] demonstrated statistical significance favoring ozone therapy, but the statistical description and lack of sample size calculation made such results questionable. Only Paoloni et al.[16] satisfactorily described the statistical analysis. However, it is the only study using placebo for comparison.

No study selected in this review assessed pain recurrence. In another systematic review,[31] pain recurrence was considered in an observational study comparing ozone with postural reeducation, and the ozone group was reported as having the best response to pain recurrence.[32] Although the studies selected in our review did not consider pain recurrence, we could note its presence by looking at the tables showing decreased pain relief in the groups during follow-up.

In our results, only the study by Canovas et al.[17] reported the degree of patient satisfaction using a global impression scale for change in pain (1–7 range). The authors did not mention this scale in their study, which led us to conclude that it was created by them based on subjective pain analysis.

The study by Paoloni et al.,[16] who used the Backill questionnaire to assess changes in quality of life during low back pain treatment showed a significant mean difference of 10.3 and 8.9 in favor of ozone at three and six months, respectively, while the study by Gallucci et al.,[20] which used the Oswestry Low Back Pain Disability Questionnaire and calculated the Oswestry Disability Index (reference <20%) showed an improvement in 74% of patients in the ozone group versus 47% in the steroid group at six months ($p < 0.01$). Because they used different scales, it was not possible to perform a meta-analysis.

Canovas et al. (2009), Canovas et al. (2015), Paoloni et al. (2009), and Gallucci et al. (2007)[16–18,20] reported that ozone therapy is a safe procedure as it does not develop complications during follow-up. In another systematic review[30] some complications were reported which ranged from subcutaneous hematoma at the puncture site to vertebrobasilar systemic stroke, but this review included observational studies and case reports.

Study limitation

In this systematic review we considered data from ozone therapy procedures, methodological flaws of each selected study, and explore the possibility of heterogeneity between studies. The high risk of study bias may be a limiting factor of our results, in addition to the impossibility of acquiring full texts of some studies.

Our data indicate the need for greater methodological rigor in randomized controlled trials regarding the use of ozone therapy for low back pain treatment. We suggest that allocation concealment, blinding of participants and personnel, and sample size calculation should be taken into consideration when designing new studies that may indicate or contraindicate this form of therapy.

Conclusion

The systematic review has shown that ozone therapy used for six months for lumbar pain relief is more effective than other therapies; however this result is not definitive as data from studies with moderate to high risk of bias were used.

Conflicts of interest

The authors declare no conflicts of interest.

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