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Research Article

Effectiveness of Paravertebral Ozone Therapy in Individuals with Low Back Pain with or without Radicular Pain: A Systematic Review

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Abstract

Objective: To analyze the efficacy of infiltrations with ozone in paravertebral muscles in individuals with low back pain with or without radicular pain.

Methods: A systematic search was conducted in electronic databases such as PUBMED, SCOPUS, SCIELO, DIALNET and other sources including Google Scholar, from January 2000 to December 2019, using the terms: ozone "or" ozone therapy "or" ozone injections "or" ozone infiltrations "and" low back pain "or" lumbar disc herniation.

Results: A total of 254 citations were identified, 59 studies were analyzed in full text, and nine studies were eligible: four observational studies and five clinical trials. In the studies analyzed it was reported that infiltrations with ozone in paravertebral muscles were effective in reducing acute and chronic low back pain, in the short, medium and long term. No side effects or serious adverse reactions were reported in any of the individuals treated. All the studies included presented poor methodological quality and / or high risk of bias.

Conclusions: Infiltrations with ozone in paravertebral muscles appear to be effective tool for the management of low back pain with or without radicular pain. However, due to the low methodological quality of the studies included, it is not possible to recommend this intervention as part of the first line of treatment for low back pain. Clinical trials with adequate methodology to clarify the effectiveness and safety of this intervention are necessary.

Impact: The results of this review indicate that paravertebral ozone therapy could be a tool to control low back pain with or without associated radicular pain in people who have undergone other conventional therapies without success.

Keywords: Herniated disc; Low back pain, Ozone

Introduction

The low back pain is an extremely frequent health problem, with an incidence of 36% and with one-year recurrence of 50% [1]. The prevalence in one year can reach up to 56% and the prevalence during life is 84% [1,2]. The etiology of low back pain is multifactorial and it is classified based on the mechanism of injury, etiological diversity, time of evolution and degree of radicular involvement [3]. Although there are various treatment modalities for this pathology, there is no standard or specific treatment for it. A conservative treatment represents the first line of action in individuals with chronic low back pain [4,5]. On the other hand, multidisciplinary rehabilitation programs [6] including

exercise [7,8] and some physical therapeutic modalities such as heat, electrotherapy and laser represent the main non-invasive treatments [5]. Likewise, current pharmacological treatment includes the use of non-steroidal anti-inflammatories in short cycles to control acute and subacute pain [5,9], the use of muscle relaxants in the presence of spasms [5] and as a second line with certain restrictions, the use of opioids and neuromodulators [6,10,11].

When a non-invasive treatment is ineffective, evidence-based guidelines recommend other intervention techniques such as epidural steroid infiltration [12,13]; that is the most effective intervention in reducing pain in the short-term in individuals with low back pain secondary to herniated disc [14]. Nevertheless, the epidural steroid infiltration in individuals with radiculopathy or lumbar stenosis is still controversial [15]. Other procedures for treating low back pain include: Facet infiltrations [12,13,16], botulinum toxin injection into lumbar paravertebral muscles [17], local anesthetics infiltration [18], infiltration of ligaments and facets with hypertonic dextrose (prolotherapy) [19] and infiltration of an oxygen-ozone mixture [20] with little evidence of its effectiveness.

The ozone application has been used in the treatment of low back pain secondary to herniated disc with or without sciatic irradiation [21,22] and other pathologies such as degenerative spinal disease [23], spinal stenosis [24] and failed surgery syndrome [25]. Ozone applications are performed in various ways: intradiscal (most used and most effective) [26-28], intraforaminal [29,30] and infiltrations into lumbar paravertebral muscles [20,21]. However, due to the little and controversial scientific evidence of the use of ozone infiltration in paravertebral muscles in individuals with low back pain, it has been classified as a complementary therapeutic intervention. Therefore, we conducted a systematic review with the objective of analyzing the efficacy, application characteristics and side effects and / or adverse reactions of intramuscular infiltrations with ozone in lumbar paravertebral muscles in individuals with acute or chronic low back pain, with or without radicular pain.

Methods

For this study, we followed the PRISMA Reporting Guidelines for Systematic Review and Meta-analysis [31].

Study Selection

This review included controlled clinical trials and observational studies (cases - controls, case series) where the therapeutic intervention was Intramuscular Infiltrations of Ozone in Lumbar Paravertebral Muscles (IIOLPM), as a treatment for individuals with low back pain with or without sciatica data. We excluded animal model studies, reviews, case reports, as well as studies where the treatment included IIOLPM and a concomitant treatment with other forms of ozone application (intradiscal, intraforaminal infiltrations or systemic applications).

Types of participants

The studies selected evaluated individuals with a clinical diagnosis of acute or chronic low back pain, with or without radicular pain, with the presence of pain and functional alterations. All participants were at least 18 years of age.

Types of intervention

Studies in which individulas were treated with one or more IIOLPM procedures were included. In clinical trials, individuals in the comparison groups were treated with placebo interventions, drug treatment, physiotherapy, exercise programs, and epidural steroid infiltrations; other co-interventions were allowed, provided they were uniform in all groups.

We excluded studies where treatment with IIOLPM was applied combined with infiltrations in another anatomical location (intradiscal, intraforaminal) or with other forms of ozone application (rectal insufflation, autohemotherapy), as well as studies where co-interventions were not uniformally performed in all study groups. Only studies that described in detail the intervention performed, the forms of evaluation and their results were chosen.

Measurement of results

We included studies that expressed their results through the evaluation of self-reported pain. Their results had to be evaluated in terms of pain reduction according to the Visual Analogue Scale (VAS) or in terms of the individual's improvement and / or resolution of symptoms. The results were categorized according to the follow-up time, in the short-term (<6 weeks), medium-term (10-12 weeks) and long-term (>24 weeks).

Data sources and searches

We performed an exhaustive search using the electronic databases PUBMED, SCOPUS, SCIELO, DIALNET and other electronic sources including Google Scholar. This search ranged from January 2000 to December 2019. We used the following keywords: ozone "or" ozone therapy "or" ozone injections "and" low back pain "or" lumbar disc herniation "and various combinations between them.

Evaluation of the risk of bias and methodological quality of the studies included

Based on the Cochrane Handbook for Systematic Reviews recommendations, version 5.1 [32] two investigators independently assessed the methodological quality and risk of bias of the clinical trials included. The following domains were evaluated: generation of random sequence (selection bias), allocation concealment (selection bias), blinding of participants and staff (performance bias), blinding of outcome assessment (detection bias), incomplete

outcome data (attrition bias), selective reporting (report bias) and other biases. The risk of bias for each domain was classified as low, high, or uncertain. A trial was considered to have low bias risk only when all domains were rated as low. If 1 or 2 domains were classified as high or uncertain risk of bias, the trial was considered to have a moderate bias risk; if 3 or more domains were classified as high or uncertain risk of bias, then it was considered a trial with high bias risk. The evaluation summary of the risk of bias is shown in Figure 1.

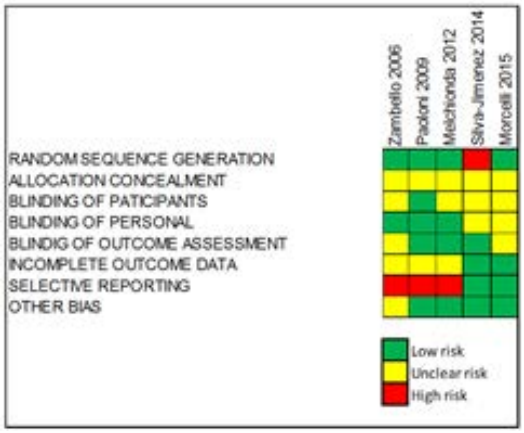


Figure 1: Summary of assessment for risk of bias in included clinical trials.

The methodological quality evaluation of the observational studies was done using the Coleman scale [33], which consists of 10 scoring domains separated in 2 parts. Part A consists of 7 domains (sample size, follow-up time, number of procedures performed, study design, diagnostic certainty, description of the conservative procedure given and description of post-intervention rehabilitation). Part B consists of 3 domains (criteria to evaluate the results, procedures to evaluate the results and description of the subject selection process). The minimum score is 0 and the maximum score is 100. For our study, we adapted this scale to non-surgical procedures as described by Abdul-Wahab, et al. [34]. The methodological quality was classified according to the score obtained [34]: <70 points = poor, >70 but <80 points = fair, >80 but <90 points = good, >90 points = excellent. The summary of the methodological quality evaluation of observational studies is shown in Table 1.

Criteria	Romeo 2011 [38]	Apuzzo 2014 [35]	Biazzo 2018 [36]	Ozcan 2019 [37]
Part A				
Sample Size	7	10	4	10
Follow time	0	5	0	2
Number of procedures	0	0	0	0
Stdy design	10	0	0	0
Diagnostic certainty	5	5	5	5
Description of the treatment technique	5	5	5	5
Description of the rehabilitation	10	10	0	0
Part B				
Results criteria	2	6	10	10
Evaluation of results	5	10	0	4
Description of the subject selection process	0	8	8	8
Total score	**44**	**59**	**32**	**44**

Table 1: Summary of the methodological quality evaluation of observational studies with Coleman Scale.

Data extraction and quality assessment

Two reviewers independently examined titles, abstracts and full texts and determined the eligibility of each study. For the eligible studies, data were extracted independently: study design, risk of bias, clinical configuration, characteristics of the participants, characteristics of the interventions, results, duration of follow-up and adverse reactions.

Data synthesis and analysis

It was not possible to perform the quantitative analysis of the clinical trials, due to the high variability in their expression of results, insufficient data to perform the analyses and high risk of bias of the studies. To homogenize and analyze the results, the percentage of improvement was calculated by comparing the level of pain reported during the initial evaluation versus the final evaluation (initial EVA mean - final EVA mean) / initial EVA mean) in the studies that reported their results this way. On the other hand, in studies where the results were reported as a percentage of individuals who presented remission of symptoms or improvement, this value was taken as a percentage of efficacy, according to the criteria of improvement established in each study.

Role of the Funding Source

This study was not funded by any institution.

Results

A total of 254 citations were identified; of those, 146 were duplicates. The titles and abstracts of the remaining 108 studies were examined, then we excluded 59 studies that were basic or animal model studies, editorials, comments and others. Fifty-nine studies were studied in full text, of which 50 were excluded for the following reasons: review studies (n=10), case reports (n=7), studies in which different infiltrations were applied to the paravertebral intramuscular modality lumbar or concomitantly applied to other forms of ozone application (n=33). In the end, nine studies, four observational studies [35-38] and five clinical trials [39-43] were eligible for inclusion in this systematic review. The included studies resulted in a high risk of bias and low methodological quality. The flow chart of the systematized search is shown in Figure 2.

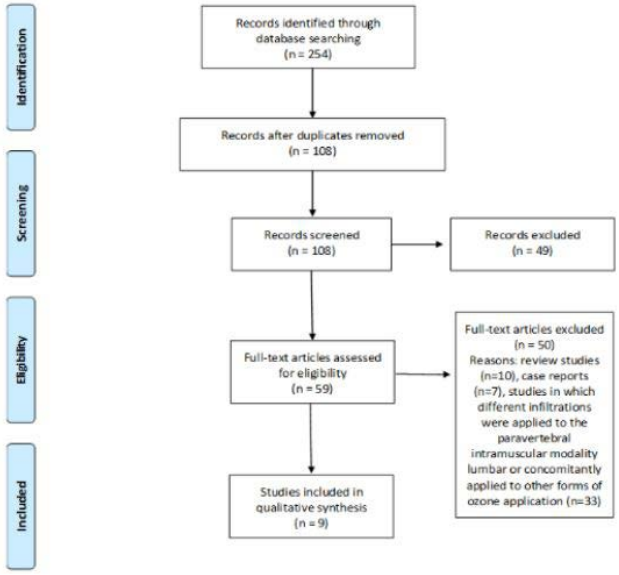


Figure 2: Systematic Review´s Flow Diagram.

The observational studies comprised 603 individuals diagnosed with low back pain with or without radicular pain who were treated with IIOLPM and 84 controls. The clinical trial comprised 308 individuals diagnosed with low back pain with or without radicular pain who were treated with IIOLPM and 234 controls who received other treatments such as drug treatment, physiotherapy and / or physical exercise programs, as well as placebo infiltrations and epidural infiltrations with corticosteroids. The characteristics of studies ar showed in Table 2.

Author, year, design and evidence level	Intervention	Evaluation and results	Adverse reactions and complications	Possible limitations
Apuzzo et al. (2014) [35] Observational retrospective case – control study, which included 546 patients (mean age of 50 years) with chronic low back pain (evolution 6 to 60 months) secondary to disc protrusion diagnosed by magnetic resonance imaging. Level Evidence III.	O3 Group: 109 patients treated with 12 sessions of IIOLPM, applying 15cc of ozone on each side of the spinous process corresponding to the affected level, at a concentration of 20mcg / ml. KT Group: 54 patients completed 12 sessions twice a week of kinesiotherapy program. O3 / KT Group: 383 patients treated with the same scheme that O3 group + kinesiotherapy program.	The results were expressed as pain reduction with VAS at the end of the 12 treatment sessions (6 weeks). KT O3 O3/KT Basal 7.4 8.6 8.5 6 weeks 4 2.7 2.9 Reporting statistically significant improvement in the mean pain reduction.	An incidence of side effects of 1.4% (7 cases) was reported in patients receiving paravertebral ozone treatment. The main side effects were: insomnia, itching and papules around the point of infiltration, dizziness and tachycardia.	The results are not explicitly reported. The treatment groups were not randomly assigned. Baseline statistical tests showed significant differences between groups.
Biazzo et al. (2018) [36] Observational retrospective case series study, which included 24 patients (mean age of 66.2 years) with chronic low back pain with or without radicular pain, (6.5 years of evolution, (range 1-20), secondary to protruding herniated disc, lumbar canal stenosis, spondylolisthesis or history of spine surgery. Level Evidence IV.	24 patients treated with 12 sessions of IIOLPM (2 per week), applying 20cc of ozone on each side of the spinous process of the affected level, at a concentration of 27mcg / ml.	The results were expressed in terms of pain reduction with VAS at 4 weeks of follow-up. VAS Basal 5.6 4 weeks 3.3 The results were expressed only in descriptive terms.	Absence of complications or adverse effects.	Without control group The scales were applied retrospectively and there could be memory bias in patients.
Ozcan et al. (2019) [37] Observational retrospective case series study, which included 62 patients (mean age of 51.9 years) with chronic low back pain (9.1 months of evolution, ranges 3 to 24 months) secondary to herniated disc, degenerative disc disease, spondylolisthesis, spinal stenosis, or unspecified pain with or without root compression. Level Evidence IV.	62 patients treated with 6 sessions of IIOLPM (1 per week), applying 50cc of ozone in the lumbosacral region at a concentration of 15mcg / ml.	The results were expressed in terms of pain reduction with VAS at 4 and 12 weeks of follow-up VAS Basal 8.2 (1.18) 4 weeks 3.10 (1.4) 12 weeks 3.22 (1.5) Statistically significant decrease in pain and disability were reported at 4 and 12 weeks of follow-up.	Mild ecchymosis was observed at the injection site in 14 of the 62 patients who underwent paravertebral injection. No other complications were observed.	Without control group.

Romeo et al. (2001) [38] Observational case - control study, which included 55 patients (30 - 55 years), diagnosed with lumbosacral pain secondary to herniated disc of small or moderate size at levels L3-L4, L4-L5 and L5-S1, without radicular involvement (by electromyographic), that did not respond to pharmacological or physiotherapeutic treatment. Level Evidence III.	O3 Group: 25 patients treated 10 sessions of IIOLPM, applied to 2cm. on each side of the spine process corresponding to the affected level. In each application 15cc was supplied. of ozone at an incremental concentration that was 6-20mcg / ml. applied twice a week. O3 / KT Group: The same scheme for O3 group + Kinesiotherapy program.	The results were expressed as a percentage of patients who presented pain reduction at the end of the treatment period (5 weeks): O3 Total elimination of pain. 60% Partial elimination of pain. 30% Without changes. 10% O3 / KT Total elimination of pain. 70% Partial elimination of pain. 20% Without changes. 10%	The absence of side effects was reported in patients treated with ozone.	No statistical comparison of baseline characteristics between groups was performed. No pain evolution time was specified.
Zambello et al. (2006) [43] Clinical trial that included 351 patients with chronic lumbosacral pain with radicular irradiation, secondary to disk pathology diagnosed by magnetic resonance imaging and with failure in conventional pharmacological treatment. Level Evidence II.	O3 Group: 180 patients treated with 1 - 3 sessions of IIOLPM, applied to 2cm. on each side of the spiny process corresponding to the affected level, as well as in the immediate upper and lower level. In each application 5cc was supplied of ozone at a concentration of 10 - 20mcg / ml. EPI Group: 171 patients treated with 1 to 3 epidural infiltrations with 80mg. of Triamcinolone in the intervertebral space corresponding to affected disc.	The results were expressed as a percentage of patients who presented pain reduction at 3 weeks of follow-up: O3 Group Total elimination of pain: 72.7% Pain reduction by 75-50%: 15.5% Pain reduction by 50-30%: 7.9% Pain reduction by <30%: 3.9% EPI Group Total elimination of pain: 45.0% Pain reduction by 75-50%: 28.0% Pain reduction by 50-30%: 12.8% Pain reduction by <30%: 14.2%	Absence of complications or serious adverse effects was reported in patients of both groups.	No randomization procedure was established and there is no description of whether there was blinding of groups or evaluators.

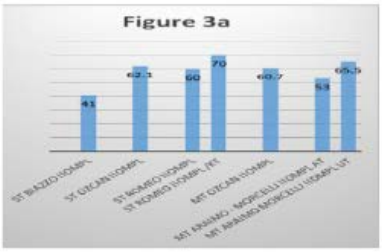
Silva-Jiménez et al. (2014) [42] Clinical trial, which included 43 patients, of average age of 45.8 (8.1), with chronic low back pain, with diagnoses of myofascial pain, facet syndrome, radicular compression due to different degrees of discopathy or by lateral recess syndrome confirmed by magnetic resonance imaging. Level Evidence II.	O3 Group: 22 patients treated with 8 sessions of IIOLPM (2 per week), applying 10cc of ozone on each side of the spinous process according to the affected level, at a concentration of 20mcg / ml. In addition, they applied 5ml of ozone at a concentration of 10-20mcg. in trigger points located in lumbar or lower limb muscles + pharmacological and physiotherapeutic treatment for 1 month. PHA/PHT Group: 21 patients treated only with pharmacological and physiotherapeutic treatment for 1 month.	Results expressed in terms of pain reduction with VAS at 2 and 4 weeks of follow-up. O3 PHA/PHT Basal 7.50 (1.14) 6.95(1.63) 2 weeks 3.27 (1.67) 3.85(1.46) 4 weeks 1 2.60(2.28) Statistically significant differences in pain reduction and improved functionality in both groups, but differences in favor of the ozone treated group.	All patients treated with ozone reported burning pain at the time of application lasting 15 min. 2 patients presented hypotension during the application.	There was no randomization of the groups. No comparative statistical analysis of baseline characteristics was performed.
Araimo-Morcelli et al (2015) [39] Clinical trial, which 50 patients with chronic low back pain who did not respond to drug treatment. Age 58.36 (9.8) years in group with anatomical technique application. 57.08 (10.6) years in group with ultrasound guidance application. Level Evidence II.	O3 UT Group: 25 patients treated with 10 sessions of IIOLPM (1 per week), applying 5cc of ozone to each side of the spinous process of the affected level, at a concentration of 20mcg / ml. with ultrasound guidance. O3 AT Group: The same scheme t for O3 UT Group but applying 10cc of ozone with anatomical technique.	The results were expressed in terms of pain reduction with VAS at 10 weeks of follow-up. PAIN O3 UT O3 AT Basal 6.44(1.29) 6.48(1.58) 10 weeks 2.22(1.95) 3.04(2.50) Statistically significant decrease in pain was reported in both treatment groups.	Discomfort was reported in all treated patients, expressed as a feeling of heaviness or burning, significantly less discomfort in the group where ozone was applied with ultrasound guidance.	It was not reported if we were other interventions during the treatment.
Paoloni et al. (2009) [41] Clinical trial, which included 60 patients (mean age of 48.8 years in the study group and 47.2 years in the control group) with acute low back and radicular pain (<10 days evolution), clinical data of neurotension and magnetic resonance disc protrusion. Level Evidence II.	O3 Group: 36 patients treated with 15 sessions of IIOLPM (3 per week), applying 10cc of ozone on each side of the spinous process corresponding to the affected level, at a concentration of 20mcg / ml. PL Group: 24 patients treated with 15 sessions of simulated injections in paravertebral muscles (3 per week), with the same scheme as in the ozone group.	The results were expressed as % of patients who had a total elimination of pain at 2,4,6,12 and 24 weeks of follow-up: O3 PL 2 weeks 0% 0% 4 weeks 5.6% 0% 6 weeks 11.1% 0% 12 weeks 38.9% 8.3% 24 weeks 61.1% 33.3% Statistically significant differences were reported in the number of patients who had a total elimination of pain, in favor of the O3 group.	Absence of complications or adverse effects was reported in patients of both groups.	It was not reported whether the patients underwent any treatment during the follow-up period.

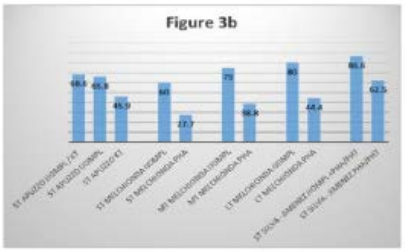
Melchionda et al. (2012) [40] Clinical trial, which included 38 patients (mean age of 53.2 (12.5) years in the study group and 52.7 (10.3) years in the control group) with acute low back and radicular pain (<1 month evolution), secondary to L4–L5 and L5-S1 disc herniation diagnosed by magnetic resonance, with clinical and / or electromyographic data of acute radiculopathy L5 or S1. Level Evidence II.	O3 Group: 20 patients treated with 12 sessions of IIOLPM (3 per week), applying 10cc of ozone on each side of the spiny process L4 or L5 according to the level affected, at a concentration of 40mcg / ml. PHA Group: 18 patients treated with parenteral and oral anti-inflammatory drugs.	The results were expressed in the number of patients who reached a value < 4 of VAS (basal 8.4 IN O3 group and 8.1 IN PHA group) at 4, 12 and 24 weeks of follow-up. O3 PHA 4 weeks 12 5 12 weeks 15 7 24 weeks 16 8 Statistically significant differences were reported in the number of patients who presented a favorable response, in favor of the O3 group at 12 and 24 weeks.	A case of syncope was reported in the ozone group. In the PHA group, 2 cases of adverse gastrointestinal effects and 2 cases of alterations in blood pressure were reported.	It was not reported whether the patients underwent any treatment during the follow-up period.
IIOMPL: Intramuscular Infiltrations with Ozone in Lumbar Paravertebral Muscles; O3: Ozone; KT: Kinesiotherapy; PHA: Pharmacotherapy; EPI: Epidural Infiltration; PL Placebo; PHT: Physiotherapy; AT: anatomical technique; UT: ultrasound technique; VAS: Visual analogue scale.				

Table 2: Design characteristics, interventions performed, evaluations, results and side effects.

Efficacy of IIOLPM according to type of intervention

In four studies [36-39], all groups were treated with interventions that included IIOLPM, and a significant percentage of pain improvement was found when comparing basal evaluations vs. short and medium term evaluations (Figure 3a). Three studies [35,40,42] compared IIOLPM vs. non-invasive treatments such as kinesiotherapy, physiotherapy and pharmacological treatment, and the percentage of pain improvement was in favor of the groups treated with IIOLPM at short, medium and long term (Figure 3b). Two studies compared IIOLPM vs. invasive treatments such as placebo infiltrations [41] and epidural infiltrations with corticosteroids [43], and the percentage of pain improvement was in favor of the groups treated with IIOLPM at short, medium and long term (Figure 3c).





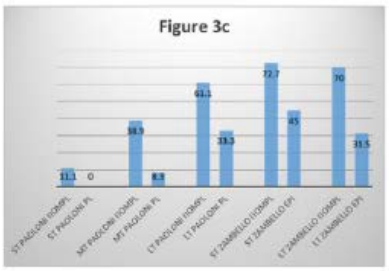
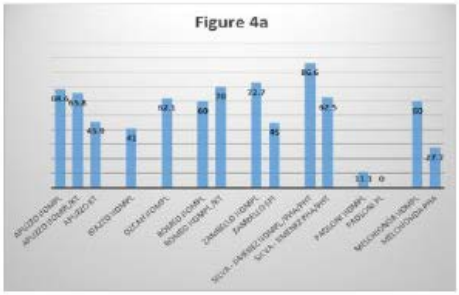
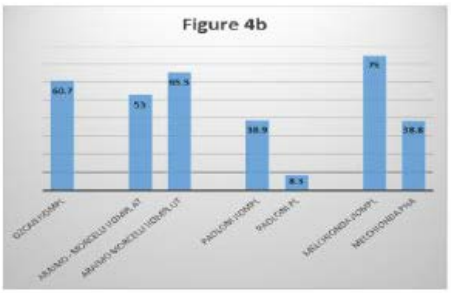


Figure 3: Percentage of decrease in pain according to the type of intervention. 3a only IIOLPM groups; 3b IIOLPM vs non-invasive treatments; 3c IIOLPM vs invasive treatments. Abbreviations: ST: Short Term; MT: Medium Term; LT: Long Term; IIOMPL: Intramuscular Infiltrations with Ozone in Lumbar Paravertebral Muscles; O3: Ozone; KT: Kinesiotherapy; PHA: Pharmacotherapy; EPI: Epidural Infiltration; PL: Placebo Infiltration; PHT: Physiotherapy; AT: Anatomical Technique; UT: Ultrasound Technique.

Efficacy of IIOLPM according to follow-up time

Eight studies [35-38,40-43] followed up in the short term and in all of them the percentage of pain improvement was significant when comparing baseline evaluations vs. short term evaluations in favor of the groups treated with IIOLPM (Figure 4a). Four studies [37,39-41] followed up in the medium term and in all of them the percentage of pain improvement was significant when comparing baseline evaluations vs. medium term evaluations in favor of the groups treated with IIOLPM (Figure 4b). Three studies [40,41,43] followed up in the long term and in all of them the percentage of pain improvement was in favor of the groups treated with IIOLPM (Figure 4c).





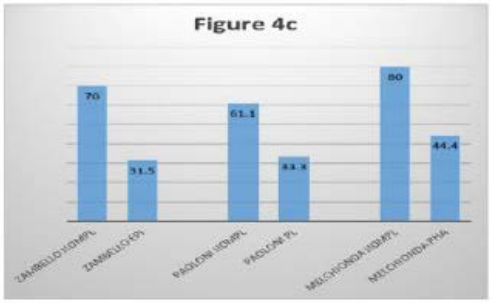
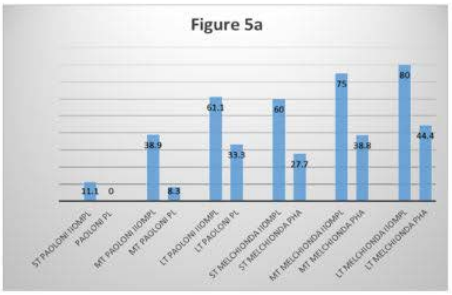
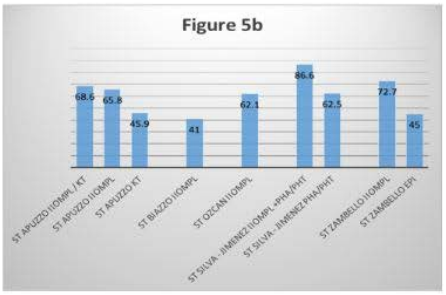


Figure 4: Percentage of decrease in pain according to the follow-up time. 4a short-term follow-up; 4b medium-term follow-up; 4c long-term follow-up. Abbreviations: IIOMPL: Intramuscular Infiltrations with Ozone in Lumbar Paravertebral Muscles; O3: Ozone; KT: Kinesiotherapy; PHA: Pharmacotherapy; EPI: Epidural Infiltration; PL: Placebo Infiltration; PHT: Physiotherapy; AT: Anatomical Technique; UT: Ultrasound Technique.

Efficacy of IIOLPM according to time of evolution

Two studies evaluated the efficacy of IIOLPM in patients with acute or subacute low back pain [40,41], finding that the percentage of pain improvement was in favor of the groups treated with IIOLPM in the short, medium and long term (Figure 5a). Five studies [35-37,42,43] evaluated the efficacy of IIOLPM in patients with chronic low back pain in the short-term and the percentage of pain improvement was significant when comparing baseline evaluations vs. short term evaluations in favor of the groups treated with IIOLPM (Figure 5b). Three studies [37,39,43] evaluated the efficacy of IIOLPM in patients with chronic low back pain in the medium and long term, finding that the percentage of pain improvement was significant when comparing baseline evaluations vs. medium or long term evaluations in favor of the groups treated with IIOLPM (Figure 5c).





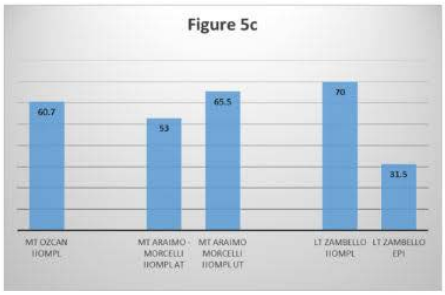


Figure 5: Percentage of decrease in pain according to the evolution of pain. 5a acute pain; 5b chronic pain at short-term; 5c chronic pain at medium and long term. Abbreviations: ST: Short Term; MT: Medium Term; LT: Long Term; IIOMPL: Intramuscular Infiltrations with Ozone in Lumbar Paravertebral Muscles; O3: Ozone; KT: Kinesiotherapy; PHA: Pharmacotherapy; EPI: Epidural Infiltration; PL Placebo Infiltration; PHT: Physiotherapy; AT: Anatomical Technique; UT: Ultrasound Technique.

Frecuency and type of application

With regards of the application characteristics of paravertebral ozone, we found a mode of 12 total applications per patient treated, with a range of 1 to 15 applications. These were applied with a frequency of 1 to 3 times per week with a mode of 2. The volume of gas used per application had a mode of 10ml (range 5-20 ml), at a concentration between 15 and 40 mcg/ml, with a mode of 20 mcg/ml. On the other hand, the application technique used in all studies was intramuscular injections in the lumbar paravertebral muscles, 2 cm from the spinous process of the affected level, including or not the immediate upper and lower levels; however, the depth reached by the needle was not specified in all studies.

Adverse reactions

Regarding the adverse reactions and side effects reported in individuals who received IIOLPM, four studies [36,38,41,43] reported absence of adverse reactions or side effects. Four studies [35,37,39,40,42] reported local adverse reactions such as ecchymosis, burning pain, feeling of heaviness, itching and papules; while three studies [35,40,42] reported cardiovascular adverse reactions such as tachycardia, transient headache, hypotension and syncope.

Discussion

The objective of this study was to analyze the efficacy of ozone infiltrations in paravertebral muscles in patients with low back pain with or without radicular pain.

Two studies [36,37] only included groups treated with IIOLPM without a control group, and evaluated the efficacy by comparing baseline evaluations vs subsequent evaluations, finding that in the short and medium term the improvement in pain was significant. In both studies, in addition to individuals with low back pain secondary to disc disease, they also included individuals with lumbar canal stenosis, spondylolisthesis or a history of spinal surgery with or without radicular pain, reporting good therapeutic response to treatment with IIOLPM; these results are interesting since no other study had treated patients with these diagnoses with the application of IIOLPM, which could open a therapeutic possibility of these pathologies.

Some studies compared IIOLPM vs non-invasive treatment. Two of them compared IIOLPM vs kinesiotherapy programs [35,38] finding a greater benefit in the groups treated with IIOLPM. Other studies compared IIOLPM versus pharmacological treatment [40] or combination of pharmacological treatment +

physiotherapy [42] finding a greater benefit in the groups treated with IIOLPM. Non-pharmacological measures [4,6] and non-steroidal anti-inflammatory drugs [5,9] represent the first line of treatment in case of low back pain. According to these results, the IIOLPM could be an additional treatment in case of not achieving the expected improvement with the non-invasive treatment or they could be used simultaneously.

On the other hand, two study has compared the IIOLPM versus other invasive procedures. Paoloni, et al. [41] compared the efficacy of IIOLPM against the use of placebo and reported a significantly higher percentage of individuals with resolution of acute low back pain when treated with IIOLPM compared to the placebo group. It is possible that the benefits of applying infiltrations to paravertebral muscles in individuals with low back pain could be based on the mechanical effect of needle stimulation in muscles to eliminate trigger points, as it has been reported that dry puncture is effective in pain reduction of individuals with chronic low back pain [44]. However, the study by Paoloni, et al. [41] reported greater efficacy of IIOLPMs than the "mechanical effect of the needle" of placebo injections; this could be due to the regulatory effect of oxidative stress and the restoration of local redox balance, as reported by León-Fernández, et al. [45]. Zambello, et al. [43] compared the IIOMPL versus epidural steroid infiltration in patiens with chronic low back pain with radicular pain, reporting a significantly higher percentage of individuals with pain resolution in a group treated with IIOLPM when compared to a group treated with epidural infiltration. Epidural infiltration probably represents the most commonly used interventional procedure for the treatment of low back pain that does not respond to non-invasive treatment [12,13] and IIOLPM appear to be an effective alternative.

On the other hand, the therapeutic effect of IIOLPM in patients with low back pain, apparently begins in the short term and can be maintained for up to 6 months, as reported in studies with this follow-up period [40,41,43]. Furthermore, this favorable effect can also be observed in patients with acute and chronic low back pain. Although in the majority of cases of acute low back pain will be self-limited and will be resolved within the following 6 weeks regardless of the treatment [46], the 2 studies evaluating the efficacy of IIOLPM in patients with acute low back pain reported benefits in favor of groups treated with IIOLPM.

On the other hand, the doses used were analyzed; based on the reported results, it seems that the dosage of IIOLPM to achieve therapeutic effects for treating of low back pain is 10 ml of ozone at a concentration of approximately 20 mcg/ml per application point, 2 times per week, for a total of 12 applications. However, Araimo-Morcelli, et al. [39] indicate that applications of low volumes of gas (5 ml) under ultrasound guidance, have the same effectiveness than applications of larger volumes (10 ml) with anatomical technique.

Finally, we also analyzed side reactions and / or adverse effects of the application technique. We observed that the most frequent side effects and adverse reactions were local reactions such as ecchymosis, burning pain, feeling of heaviness, itching and papules that resolved favorably, and no one had serious complications. According to the study by Araimo-Morcelli, et al. [39], adverse reactions such as local discomfort can be reduced by applying a smaller volume of gas under ultrasound guidance, with the same effectiveness as the application of larger volumes.

Only one case of paravertebral abscess has been reported in the medical literature as a complication of IIOLPM application [47]. This complication is the only severe complication observed in individuals treated with IIOLPM. In other type of applications such as intraforaminal [48], side effects such as fibrosis and soft tissue adhesions to bone structures or nerve roots to the dural sac have been reported. Regarding intradiscal application, cases of discitis [49], radicular lesions [50], septicemia [51] and even cerebral vascular event [52] have been observed; nevertheless, in a meta-analysis [21] the probability of complications secondary to intradiscal ozone application procedure was only 0.064% (95% CI, 0.000% - 0.136%), which represents a very low percentage for this modality. Based on the above mentioned, we could consider that IIOMPL applications have lower risk of complications compared with other forms of application such as intraforaminal or intradiscal. Likewise, due to the less complexity in the technique application and the less infrastructure needed, IIOMPL could be very useful and its use could facilitate the treatment of individuals with low back pain.

Although the IIOMPL is an interventional procedure for low back pain that has not been recommended in clinical practice guidelines, given its low technical complexity and low risk of adverse events, it could represent an invasive treatment option for the control of acute low back pain and chronic, when non-invasive or other interventional treatments with greater clinical evidence such as epidural corticosteroid infiltration or facet infiltration have not had the expected results.

Previous review studies have analyzed the efficacy of ozone infiltrations in reducing back pain [21,22,53,54]; nevertheless, only Magalhaes, et al. [21] included in its review 2 studies where ozone infiltrations in lumbar paravertebral muscles were used, proposing a level of evidence1B for this intervention.

In our review we found a beneficial effect of IIOLPM in reducing acute and chronic low back pain n the short, medium and long term; however, the poor methodological quality and the high risk of bias of the nine studies included, do not allow us to establish a level of evidence and recommendation for IIOLPM.

Limitations

We acknowledge that our study has some limitations. It is

important to note that all of the studies included had a high risk of bias and some had a poor methodological design. Similarly, the lack of a control group in some studies decreased the quality of the evidence. Finally, the number of studies included in this review is very small. Nonetheless, there is little scientific evidence on the subject, so we consider this work to be usefull for future clinical research studies and treatment options for individuals with low back pain.

Conclusions

Although the reported results indicate that ozone infiltrations in the lumbar paravertebral muscles were effective in reducing pain in patients with acute and chronic low-back pain in the short, medium and long term, the low methodological quality and the high risk of bias of the studies included, do not allow establishing a solid level of evidence and it is not possible to recommend it as a routine intervention in individuals with low back pain. However, the favorable results and low risk of complications reported, as well as the low technical complexity of the procedure, suggest that ozone infiltrations in lumbar paravertebral muscles could be a therapeutic tool useful in the treatment of acute and chronic low back pain when other interventions with more evidence have failed; clinical trials of good methodological quality, low risk of bias, greater number of patients and longer follow-up periods are necessary to clarify the efficacy and safety of this intervention.

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Concept/idea/research design, writing, data collection, data analysis, project management and consultation (including review of manuscript before submitting): All authors participated equally in the manuscript.

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The authors completed the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported no conflicts of interest.

References

1. Hoy D, Brooks P, Blyth F, Buchbinder R (2010) The Epidemiology of low back pain. Best Pract Res Clin Rheumatol 24: 769-781.
2. Tavee JO, Levin KH (2017) Low Back Pain. Continuum (Minneap Minn) 23: 467-486.
3. Maher C, Underwood M, Buchbinder R (2017) Non-specific low back pain. Lancet 389: 736-747.
4. Foster NE, Anema JR, Cherkin D, Chou R, Cohen SP, et al. (2018) Prevention and treatment of low back pain: evidence, challenges, and promising directions. Lancet 391: 2368-2383.
5. Qaseem A, Wilt TJ, McLean RM, Forciea MA (2017) Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline from the American College of Physicians. Ann Intern Med 166: 514-530.
6. Oliveira CB, Maher CG, Pinto RZ, Traeger AC, Lin CC, et al. (2018) Clinical practice guidelines for the management of non-specific low back pain in primary care: an updated overview. Eur Spine J 27: 2791-2803.
7. Gomes-Neto M, Lopes JM, Conceicao CS, Araujo A, Brasileiro A, et al. (2017) Stabilization exercise compared to general exercises or manual therapy for the management of low back pain: A systematic review and meta-analysis. Phys Ther Sport 23: 136-142.
8. Sitthipornvorakul E, Klinsophon T, Sihawong R, Janwantanakul P (2018) The effects of walking intervention in patients with chronic low back pain: A meta-analysis of randomized controlled trials. Musculoskelet Sci Pract 34: 38-46.
9. Wong JJ, Cote P, Ameis A, Varatharajan S, Varatharajan T, et al. (2016) Are non-steroidal anti-inflammatory drugs effective for the management of neck pain and associated disorders, whiplash-associated disorders, or non-specific low back pain? A systematic review of systematic reviews by the Ontario Protocol for Traffic Injury Management (OPTIMa) Collaboration. Eur Spine J 25: 34-61.
10. Abdel Shaheed C, Maher CG, Williams KA, Day R, McLachlan AJ (2016) Efficacy, Tolerability, and Dose-Dependent Effects of Opioid Analgesics for Low Back Pain: A Systematic Review and Meta-analysis. JAMA Intern Med 176: 958-968.
11. Shanthanna H, Gilron I, Rajarathinam M, AlAmri R, Kamath S, et al. (2017) Benefits and safety of gabapentinoids in chronic low back pain: A systematic review and meta-analysis of randomized controlled trials. PLoS Med 14: e1002369.
12. Filippiadis DK, Kelekis A (2016) A review of percutaneous techniques for low back pain and neuralgia: current trends in epidural infiltrations, intervertebral disk and facet joint therapies. Br J Radiol 89: 20150357.
13. Manchikanti L, Abdi S, Atluri S, Benyamin RM, Boswell MV, et al. (2013) An update of comprehensive evidence-based guidelines for interventional techniques in chronic spinal pain. Part II: guidance and recommendations. Pain Physician 16: S49-283.
14. Lee JH, Kim DH, Kim DH, Shin KH, Park SJ, et al. (2018) Comparison of Clinical Efficacy of Epidural Injection With or Without Steroid in Lumbosacral Disc Herniation: A Systematic Review and Meta-analysis. Pain Physician 21: 449-468.
15. Manchikanti L, Knezevic NN, Boswell MV, Kaye AD, Hirsch JA (2016) Epidural Injections for Lumbar Radiculopathy and Spinal Stenosis: A Comparative Systematic Review and Meta-Analysis. Pain Physician 19: E365-E410.
16. Vekaria R, Bhatt R, Ellard DR, Henschke N, Underwood M, et al. (2016) Intra-articular facet joint injections for low back pain: a systematic review. Eur Spine J 25: 1266-1281.
17. Waseem Z, Boulias C, Gordon A, Ismail F, Sheean G, et al. (2011) Botulinum toxin injections for low-back pain and sciatica. Cochrane Database Syst Rev. Cd008257.
18. Egli S, Pfister M, Ludin SM, Puente de la Vega K, Busato A, et al. (2015) Long-term results of therapeutic local anesthesia (neural therapy) in 280 referred refractory chronic pain patients. BMC Complement Altern Med 15: 200.
19. Dagenais S, Yelland MJ, Del Mar C, Schoene ML (2007) Prolotherapy injections for chronic low-back pain. Cochrane Database Syst Rev 2007: CD004059.

20. Bocci V, Borrelli E, Zanardi I, Travagli V (2015) The usefulness of ozone treatment in spinal pain. Drug Des Devel Ther 9: 2677-2685.

21. Magalhaes FN, Dotta L, Sasse A, Teixera MJ, Fonoff ET (2012) Ozone therapy as a treatment for low back pain secondary to herniated disc: a systematic review and meta-analysis of randomized controlled trials. Pain Physician 15: E115-E129.

22. Steppan J, Meaders T, Muto M, Murphy KJ (2010) A metaanalysis of the effectiveness and safety of ozone treatments for herniated lumbar discs. J Vasc Interv Radiol 21: 534-548.

23. Bonetti M, Fontana A, Martinelli F, Andreula C (2011) Oxygen-ozone therapy for degenerative spine disease in the elderly: a prospective study. Acta Neurochir Suppl 108: 137-142.

24. Baeza-Noci J (2007) Spinal ozone therapy in lumbar spinal stenosis. Int J Ozone Ther 6: 17-24.

25. Barbosa DC, Angelos JSD, Macena GMJ, Magalhaes FNO, Fonoff ET (2017) Effects of ozone on the pain and disability in patients with failed back surgery syndrome. Rev Assoc Med Bras 63: 355-360.

26. Giurazza F, Guarnieri G, Murphy KJ, Muto M (2017) Intradiscal O2O3: Rationale, Injection Technique, Short- and Long-term Outcomes for the Treatment of Low Back Pain Due to Disc Herniation. Can Assoc Radiol J 68: 171-177.

27. Muto M, Giurazza F, Silva RP, Guarnieri G (2016) Rational approach, technique and selection criteria treating lumbar disk herniations by oxygen-ozone therapy. Interv Neuroradiol, 22: 736-740.

28. Rahimi-Movaghar V, Eslami V (2012) The major efficient mechanisms of ozone therapy are obtained in intradiscal procedures. Pain Physician 15: E1007-1008.

29. Bonetti M, Fontana A, Cotticelli B, Volta GD, Guindani M, et al. (2005) Intraforaminal O(2)-O(3) versus periradicular steroidal infiltrations in lower back pain: randomized controlled study. AJNR Am J Neuroradiol 26: 996-1000.

30. Zhang Y, Ma Y, Jiang J, Ding T, Wang J (2013) Treatment of the lumbar disc herniation with intradiscal and intraforaminal injection of oxygen-ozone. J Back Musculoskelet Rehabil 26: 317-322.

31. Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 6: e1000097.

32. Higgins JPT, Green S (2011) Cochrane Handbook for systematic reviews of interventions version 5.1. 0.

33. Coleman BD, Khan KM, Maffulli N, Cook JL, Wark JD (2000) Studies of surgical outcome after patellar tendinopathy: clinical significance of methodological deficiencies and guidelines for future studies. Victorian Institute of Sport Tendon Study Group. Scand J Med Sci Sports 10: 2-11.

34. Abdul-Wahab TA, Betancourt JP, Hassan F, Thani SA, Choueiri H, et al. (2016) Initial treatment of complete rotator cuff tear and transition to surgical treatment: systematic review of the evidence. Muscles Ligaments Tendons J 6: 35-47.

35. Apuzzo D, Giotti C, Pasqualetti P, Ferrazza P, Soldati P, et al. (2014) An observational retrospective/horizontal study to compare oxygen-ozone therapy and/or global postural re-education in complicated chronic low back pain. Funct Neurol 29: 31-39.

36. Biazzo A, Corriero AS, Confalonieri N (2018) Intramuscular oxygen-ozone therapy in the treatment of low back pain. Acta Biomed 89: 41-46.

37. Özcan Ç, Polat Ö, Çelik H, Uçar BY (2019) The Effect of Paravertebral Ozone Injection in the Treatment of Low Back Pain. Pain Pract 19: 821-825.

38. Romeo A, Cirillo F (2001) Contributo della chinesiterapia e dell'ossigeno-ozonoterapia nel trattamento dei "conflitti" disco-radicolari lombosacrali. Rivista di Neuroradiologia 14: 47-49.

39. Araimo Morselli F, Zuccarini F, Scarpa I, Imperiale C, Guzzo F (2015) Ultrasound Guidance in Paravertebral Injections of Oxygen-Ozone: Treatment of Low Back Pain. J Pain Relief 5: 220.

40. Melchionda D, Milillo P, Manente G, Stoppino L, Macarini L (2012) Treatment of radiculopathies: a study of efficacy and tolerability of paravertebral oxygen-ozone injections compared with pharmacological anti-inflammatory treatment. J Biol Regul Homeost Agents 26: 467-474.

41. Paoloni M, Di Sante L, Cacchio A, Apuzzo D, Marotta S, et al. (2009) Intramuscular oxygen-ozone therapy in the treatment of acute back pain with lumbar disc herniation: a multicenter, randomized, double-blind, clinical trial of active and simulated lumbar paravertebral injection. Spine (Phila Pa 1976) 34: 1337-1344.

42. Silva Jiménez E, Toro M, Baíz C (2014) Eficacia de la infiltración de ozono paravertebral lumbar y en puntos gatillos como coadyuvante del tratamiento en pacientes con dolor lumbar crónico y lumbociatalgia crónica en el síndrome doloroso miofascial aislado o acompañado de otras patologías. Revista de la Sociedad Española del Dolor 21: 23-38.

43. Zambello A, Fara B, Tabaracci G, Bianchi M (2006) Epidural steroid injection vs paravertebral O_2-O_3 infiltration for symptomatic herniated disc refractory to conventional treatment: A prospective randomized study. Rivista di Neuroradiologia 5: 123-127.

44. Liu L, Huang QM, Liu QG, Thitham N, Li LH, et al. (2018) Evidence for Dry Needling in the Management of Myofascial Trigger Points Associated With Low Back Pain: A Systematic Review and Meta-Analysis. Arch Phys Med Rehabil 99: 144-152.

45. Leon Fernandez OS, Pantoja M, Diaz Soto MT, Dranguet J, Garcia Insua M, et al. (2012) Ozone oxidative post-conditioning reduces oxidative protein damage in patients with disc hernia. Neurol Res 34: 59-67.

46. Frymoyer JW, Cats-Baril WL (1991) An overview of the incidences and costs of low back pain. Orthop Clin North Am 22: 263-271.

47. Menendez P, Garcia A, Pelaez R (2014) Paravertebral and intra-abdominal abscess due to oxygen-ozone therapy for lower back pain. Rev Esp Cir Ortop Traumatol 58: 125-127.

48. Vanni D, Galzio R, Kazakova A, Pantalone A, Sparvieri A, et al. (2016) Intraforaminal ozone therapy and particular side effects: preliminary results and early warning. Acta Neurochir (Wien) 158: 491-496.

49. Fort NM, Aichmair A, Miller AO, Girardi FP (2014) L5-S1 Achromobacter xylosoxidans infection secondary to oxygen-ozone therapy for the treatment of lumbosacral disc herniation: a case report and review of the literature. Spine (Phila Pa 1976) 39: E413-E416.

50. Ginanneschi F, Cervelli C, Milani P, Rossi A (2006) Ventral and dorsal root injury after oxygen-ozone therapy for lumbar disk herniation. Surg Neurol 66: 619-620.

51. Gazzeri R, Galarza M, Neroni M, Esposito S, Alfieri A (2007) Fulminating septicemia secondary to oxygen-ozone therapy for lumbar disc herniation: case report. Spine (Phila Pa 1976) 32: E121-123.

52. Corea F, Amici S, Murgia N, Tambasco N (2004) A case of vertebrobasilar stroke during oxygen-ozone therapy. J Stroke Cerebrovasc Dis 13: 259-261.

53. de Andrade RR, Oliveira-Neto OB, Barbosa LT, Santos IO, Sousa-Rodrigues CF, et al. (2019) Effectiveness of ozone therapy compared to other therapies for low back pain: a systematic review with meta-analysis of randomized clinical trials. Rev Bras Anestesiol 69: 493-501.

54. Costa T, Linhares D, Ribeiro da Silva M, Neves N (2018) Ozone therapy for low back pain. A systematic review. Acta Reumatol Port 43: 172-181.