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Review

Ozone therapy as a complementary treatment in fibromyalgia. A systematic review

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Ozone fibromyalgia, ozone in fibromyalgia, ozone therapy fibromyalgia.

Abstract

Fibromyalgia (FM) is a chronic disease which ethology is still poorly known, diagnosed according to established the clinic and treated in a multidisciplinary way, using measures of a pharmacological and non-pharmacological nature. In this context, ozone therapy (mixture of oxygen /ozone), has been gaining notoriety in recent years as a complementary therapy in FM treatment. This study aims to analyse available evidence on effectiveness of ozone therapy in this disease, whose prevalence in Portugal and all over the world. It was used PRISMA methods to conduct this systematic review. References were searched in PubMed, ISCO3, Google Scholar and Scielo databases. Only 4 papers fulfilled inclusion criteria. All analysed articles reported improvement of symptoms and considered ozone therapy as an effective tool for FM treatment selected studies reported improvement of specific symptoms, such as pain intensity, quality of life, sleep quality, depression and anxiety symptoms. We concluded that existing evidence is insufficient to indicate ozone therapy as an effective and safe treatment in the long and/or short term for those with FM. Additional clinical studies are needed to demonstrate the effects of ozone therapy in FM

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Introduction

Fibromyalgia (FM) is a disease whose main symptom is chronic widespread pain It often has other symptoms associated with it, such as fatigue, non-restful sleep, mood disorders, anxiety, depression and cognitive changes. In general, clinical picture greatly affects quality of life of these patients. In clinical situations that occur with co-morbidities, diagnosis is complex, requires rigorous criteria and habitual confirmation is time-consuming. [1-4] Prevalence of FM is significantly higher in women than in men and epidemiological studies indicate a prevalence of 2% in the European population. In Portugal, the specific prevalence rate of FM is 1.7% (1.1%-2.1%) of the total rheumatic diseases; the vast majority of patients are female and prevalence peak is in ages range 43 and 46 years. [5,6]

Although FM aetiology is unknown, several causes have been pointed out, such as: 1st degree co-blood, pregnancy with severe oxidative stress, after severe inflammation and /or trauma, viral infections, Epstein-Barr, COMT genetic disorders (catechol-o-methyl-transferase), deficit in interleukins levels. [7,8] In FM pathogenesis is observed: alteration of microcirculation and oxygenation of the motor plaque, increase of allogenic substances such as substance P, alteration of the levels of interleukins related to states of pain and fatigue (IL-6) and inflammatory activity and immunomodulatory (IL-10) activity. [8,9]

The systematic review and meta-analyses concerned with pharmacological / non-pharmacological management for fibromyalgia conducted by The European League Against Rheumatism (EULAR – 2017) [10], came to the conclusion that size of effect for most treatments is relatively modest, and the recommendations for FM management point to individualized treatment, guided by a multidisciplinary team using pharmacological and non-pharmacological measures. Among the latter, ozone therapy is not even mentioned. Despite notorious difficulties in imposing itself in the current scientific panorama, in the last two decades, ozone therapy, have been progressively object of study and analysis in many published scientific studies, both pre-clinical and clinical. Proving the anti-inflammatory, analgesic, antioxidant and immunomodulation properties of ozone and highlighting ozone therapy beneficial effects in multiple pathologies, namely those with high oxidative stress, such as in FM. [8,11-13]

This brief study aims on one hand, to analyse ozone therapy efficacy as a complementary non-pharmacological therapy, and on the other hand, to inform on the development of a research project to be implement in the near future on our Center.

Method

We conducted a rapid review using recommendations of the Cochrane Rapid Reviews Methods Group [14]. Eligibility Criteria: We sought primary studies only to address the research question. Priority of inclusion was given to: i) individual or cluster randomised controlled trials (RCTs) and quasi-randomised controlled trials; ii) observational cohort studies; and iii) cost-effectiveness/cost-utility/cost-benefit studies. Other types of studies were also identified for consideration for inclusion in case of no or few primary studies with strong study designs could be found.

Included studies were restricted to patients over 18 years of age, diagnosed with FM. FM was defined as in 1990 ACR criteria. Ozone therapy was required to be the main intervention in the study. No restrictions were defined on the comparator. Primary outcomes were defined as measures of pain intensity, quality of life, sleep quality, depression and anxiety symptoms. Researchers believed such outcomes allowed for an understanding ozone therapy clinical impact in FM patients. Studies written on a language other than English, Spanish, Portuguese, Italian or Russian were excluded.

Search methods for identification of studies: A comprehensive search of two databases and two websites was performed. The databases explored were The International Scientific Committee of Ozone Therapy database (ISCO3) and PubMed (Medline). The websites searched were Google and Google Scholar.

Grey literature and manual search: One of the selected databases index a combination of published and unpublished studies (for example, conference abstracts and unpublished reports); therefore, unpublished studies were partially captured through the electronic search process.
Search strategy: Searches were conducted between 1st February and 15th February 2021. Articles from 1997-2021 was taking into consideration. Databases were searched using the keywords: “ozone therapy fibromyalgia” or “ozone fibromyalgia” or “ozone in fibromyalgia”. Key words were searched for in title and abstract. Results were downloaded into the EndNote reference management program (version X8) and duplicates were removed. The internet search utilised the same search terms.
Screening and selection of studies: Searches were conducted and screened according to the selection criteria by two reviewers (SR, IO). Disagreements regarding eligibility of studies were resolved by discussion and consensus. Where the two reviewers were still uncertain about inclusion, the other reviewer (DC) was asked to provide input to reach consensus. For those studies that initially appeared to meet the inclusion criteria, but did not on inspection of the full text, the reasons for their exclusion were detailed on the PRISMA flow diagram.

Data extraction: Information that was extracted from studies and reviewed included objectives, setting, recruitment of participants, sample size, clinical and demographic characterization of the sample, characteristics of ozone therapy. Data extraction was performed by one reviewer and confirmed by a second reviewer. Disagreements were resolved through discussion and consensus.

Assessment of methodological quality: The methodological quality of the non-randomised studies of interventions was assessed by one reviewer (SR) using the ROBINS-I tool.[16] This assessment includes three categories: pre-intervention, at intervention and post-intervention. Each category is assessed as 'low risk of bias', 'moderate risk of bias', serious risk of bias, 'critical risk of bias' and 'no information'.

Data analysis: Findings from the included publications were synthesised using tables and a narrative summary.

Results

Thirty-five studies were identified through database searching, whereas 3 were found through other sources. After the removal of duplicates, 27 studies were subjected to screening and of those 9 went to full text analysis. Four articles met the inclusion criteria. The reasons for exclusion of the 18 papers at full text stage are shown in Figure 1.

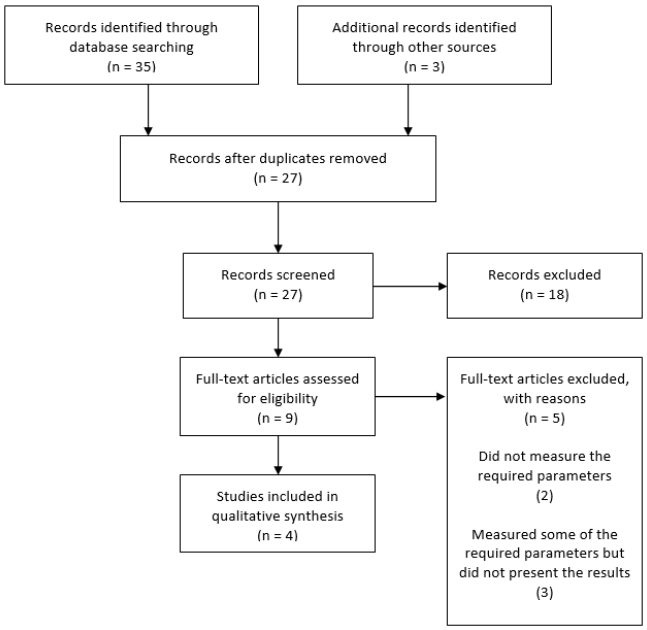

Figure 1. Study selection flow chart.

Characteristics of included studies

Our search did not find randomized controlled trials to include in the analysis. Reviewers included one nonrandomized controlled trial,[16] two nonrandomized, pre-post intervention studies,[15,18] and one case report.[17] Characteristics of all included studies are summarised in Table 1. Assessment of bias using the ROBINS-I tool is reported in Table 1 e 2.

The combined samples of the 4 included studies amounted to 107 patients. Patients were recruited from a specialized clinic in Spain,[18] and from the outpatient clinic and inpatient department of an university hospital in Egypt [16] and the remaining two did not disclose the study site. All patients were adults, and the majority was female. Disease duration was heterogenous among the studies, ranging from 0.5 to 30 years. Included studies did not consider follow-up time, as the last measurements were registered after the termination of the intervention.

Table 1. Characteristics of the included studies.

Study ID.	Study Type	Population and setting	Intervention	Comparator	Scales and Measurements
Hidalgo-Tallón *et al*. (2013)	Nonrandomized, pre-post intervention study	Total sample: 36; completed the study:35. Age (M [SD]) (y): 50 [±10]. Percentage of women: 91.7% Duration of disease (M [SD]) (y): 7.4 [±6.4] Setting: not disclosed	Cycle of 12 biweekly sessions of MAH: using a concentration of 30µg/mL first two sessions, posteriorly up to 50 µg/mL and a gas volume of 150 mL, alternate with MiAH 10 mL blood and 10 mL oxygen-ozone and RiO3.	No comparator.	FIQ, BDI, PSQI, SF-12, VAS Evaluation timing: FIQ: baseline and at weeks 4, 8, and 12; other measurements: baseline and posttreatment
Elgawish *et al*. (2015)	Nonrandomized controlled trial	Total sample: 50; Intervention (IM):20; Intervention (IM+RI):20; CG: 10 Age (M [SD]) (y): Intervention (IM) 47.5 [±4.8]; Intervention (IM+IR)	Cycle of 10 biweekly sessions. Intervention (IM): IM ozone injection in tender points 2 sessions /week for 5 weeks; concentration of 15µg/mL with volume 10 to 20 ml of gas injected in	Treatment as usual.	VAS, FIQ, SF-12, HDRS Evaluation timing: baseline, posttreatment

		45.6 [±4.2]; CG 45.2 [±3.9] Percentage of women: 100% Duration of disease (M [SD]) (y): Intervention (IM): 1.5 [±1.6]; Intervention (IM+RiO3): 1.9 [±1.1]; CG: 1.6 [±1.3]	about 7-13 tender points/session. Intervention (IM+RiO3): IM injection in tender points at a concentration of 15 µg/mL with volume 25 to 40 ml of gas injected in about 7-13 tender points/session and RiO3 of ozone therapy at a concentration of 50 µg/mL with volume up to 200 ml/twice weekly for 5 weeks.		
Balestrero *et al*. (2017)	Case Report	Total sample: 1. Completed the study:1 Age: 45. Percentage of women: 100% Duration of disease (y): 20 Setting: not	Cycle of 12 biweekly sessions of MAH: using a concentration of 30µg/mL first two sessions, posteriorly up to 50 µg/mL and a gas volume of 150	No comparator.	FIQR, FSQ (WPI and SSS) Evaluation timing: baseline, posttreatment

		disclosed	mL, alternate with MiAH 10 mL blood and 10 mL oxygen-ozone and RiO3.		
Moreno-Fernández *et al*. (2019)	Nonrandomized, pre-post intervention study	Total sample: 20; completed the study: 20. Age (M [SD]) (y): 47.5 [±11.0]. Percentage of women: 100% Duration of disease (M [SD]) (y): 13.6 [±9.2] Setting: Specialized Clinic, Seville, Spain	Cycle of 10 biweekly sessions of MAH: the first three sessions' dose was 30 μg/ml, 40 μg/ml for the fourth, 50 μg/ml for the fifth, and 60 μg/ml for the last five, and a gas volume of 150 mL.	No comparator.	FIQ Evaluation timing: baseline, posttreatment (1 week)
BDI stands for Beck Depression Inventory; FIQ, Fibromyalgia Impact Questionnaire; FIQR, Fibromyalgia Impact Questionnaire-Revised; FSQ, Fibromyalgia Survey Questionnaire; HDRS, Hamilton depression rating scale; IM, local intra-muscular ozone injection; RiO3, rectal insufflation; CG, control group; MAH, major autohemotherapy; MiAH, minor autohemotherapy, PSQI, Pittsburgh Sleep Quality Index; SF-12, Short-Form Health Survey; SSS, Symptoms Severity Scale; STAI, State and Trait Anxiety Inventory; VAS, Visual Analogue Scale; WPI, Widespread Pain Index					

Table 2. The ROBINS-I tool for assessing risk of bias of observational studies included in the rapid review.

Study ID.	Pre-intervention		At intervention	Post-intervention				Total Score
	Confounding bias	Selection bias	Classification Bias	Deviation Bias	Missing data bias	Measurement of outcome bias	Selective reporting Bias	Overall risk of bias judgement
Hidalgo-Tallón *et al*. (2013)	Serious risk	Serious risk	Low risk	Low risk	No information	Serious risk	Moderate risk	Serious risk[a]
Elgawish *et al*. (2015)	Serious risk	Serious risk	Moderate risk	No information	No information	Serious risk	Moderate risk	Serious risk[a]
Moreno-Fernández *et al*. (2019)	Serious risk	Critical risk	Moderate risk	No information	No information	Serious risk	Moderate risk	Critical risk[b]

[a] Serious risk: the study is judged to be at serious risk of bias in at least one domain, but not at critical risk of bias in any domain; [b] The study is judged to be at critical risk of bias in at least one domain.

Description of the intervention

Of the four articles selected, only one study includes comparators (study of Elgawish et al.) [16]. Two other studies did not conclude comparators [15,18], and was also evaluated a case report [17].

Summary of Findings

Pain Intensity: Pain Intensity was assessed in all included studies. It was measured using the visual analogue scale (VAS) in 3 included studies [15,16,18] and with Widespread Pain Index (WPI) and Symptom Severity (SS) scale in one study [17].

The 3-armed study of Elgawish et al. observed statistically significant reduction in VAS by 45.3 % ± 9.1% ($p<0.001$) on pain in patients who received ozone therapy by local intra-muscular injection and rectal insufflation (group B), compared with control group (C) 17.7 % ± 1.4% ($p=0.04$) and 35.3 % ± 5.1% ($p<0.001$) in patient group who received the ozone therapy by local intra-muscular injection (group A) [16]. Moreno-Fernández, A., et al. showed decrease of tender points, from 14.9 (±3.1) to 7.0 (±2.1) [18]. Hidalgo-Tallón et al. reveals a statistically significant reduction in pain. Average pain score at baseline was 55.5[±35.6]. At week 4 (41.2 [±30.2]). At week 8 and week 12, there was a decrease in pain scores, 41.2 [±32.3] and 31.6 [±29.6], respectively. Overall decrease of pain scores from baseline to endpoint achieve statistical significance ($p=0.0003$). [15]

The case report mentioned a reduction in pain. Average pain score at baseline was, SSS=7, WPI=15; after treatment, SSS=1, WPI=7. The authors also reported "reduction in values obtained using the VAS scale in individual areas of the body". No measurements were made available.[17]

Quality of Life: All included studies considered the impact of ozone therapy in quality of life, using the FM impact questionnaire (FIQ). [15-18] The 3-armed study of Elgawish et al. showed a significant decrease in FIQ total scores after 5 weeks of treatment in groups (A&B) with percentage of change 33.4 % in group (A) and 47.7% in group (B) more than in control group (C)17.3 %. [16]. Moreno-Fernández, A., et al. showed decrease of FIQ total score, from 54.6 (±11.3) to 37.2 (±10,6) [18].

Hidalgo-Tallón et al. reports a reduction from baseline 67.8 [±18.0] to endpoint which was statistically significant ($p=0.0002$) with small effect sizes at week 4 (57.7[±20.3]), ($d=0.57$), week 8 (58.8[±20.9]), ($d=0.50$) and week 12 57.7[±20.3]), ($d=0.42$). [15] The case report mentioned a decrease of FIQ total score, from 58 to 46 [17].

Quality of Sleep: Quality of sleep was assessed in all included studies, but only one study use the Pittsburgh Sleep Quality Index (PSQI).[15] There was a decrease in the PSQI mean from baseline (14.4 [± 3.8]) to endpoint (12.8 [±4.5]), which was statistically significant ($p=0.021$), with small effect sizes ($d=0.42$). [15]

The morning tiredness domain of the Fibromyalgia Impact Questionnaire (FIQ) was used as a measurement for quality of sleep in 2 studies [15,16] and both reported improvements. Hidalgo-Tallón et al. reports a reduction from baseline (57.6 [±35.3]) to endpoint (41.1[±33.9]), which was statistically significant (p=0.0045) with small effect sizes at week 4 (d=0.45), week 8 (d=0.46) and week 12 (d=0.47). The 3-armed study of Elgawish et al. showed a reduction of 22.4±2.7% (p<0.001) in the morning tiredness in patients who received the ozone therapy by local intra-muscular injection, whereas the combination of ozone therapy by local intra-muscular injection and rectal insufflation attained a reduction of 28.4±2.4% (p<0.001).[16] The patients on the control arm also experienced a reduction of 13.2±5.1% (p<0.001) in the morning tiredness domain. [16]

The two remaining studies mentioned an improvement in the quality of sleep, though the measurements used are not explicit. [17,18]

Depression: Three studies considered the effect of ozone therapy in depressive symptoms. [15-17] The case report mentioned a clear improvement of mood, though no measurements are made available.[17] Hidalgo-Tallón et al. reveals a statistically significant (p=0.0002) reduction in the Beck Depression Inventory (BDI) scores from baseline (23.1[±10.5]) to endpoint (18.4[±9.1]) with small effect sizes (d=0.45). The analysis of FIQ depression domain also noticed a decrease in mean scores from baseline (43.1 [±34.8]) to endpoint (31.1[±30.2]) with small effect sizes at week 4 (d=0.18), week 8 (d=0.27) and week 12 (d=0.34), though it did not find statistical significance (p=0.1720).

Elgawish et al. observed statistically significant reductions in the FIQ depression domain in all study arms. Patients who received ozone therapy by local intra-muscular injection reported a reduction of 15.7±1.3% (p<0.001), while those who received a combination of ozone therapy by local intra-muscular injection and rectal insufflation displayed a reduction of 20.0±2.3% (p<0.001). The control group also observed a reduction of 14.7±0.7 % (p<0.001). Depression was also evaluated through the Hamilton depression rating scale (HDRS). Patients on local intra-muscular injection therapy showed a reduction of 3.1±0.4% (p=0.04), surpassed by those on the combined therapy with reductions of 5.7±1.4% (p<0.001). The controls also displayed a reduction, albeit slightly smaller, of 2.7±0.3% (p=0.04).

Anxiety: Three studies considered ozone therapy impact in anxiety symptoms [15-17]. In the case report, patient anxiety scores were not made available, though the authors state that anxiety was still evident after the intervention [17]. Hidalgo-Tallón et al. reported anxiety scores based on FIQ's anxiety domain [15]. Average anxiety score at baseline was 46.2[±36.9]. Authors report a reduction in anxiety, particularly at week 4 (34.9 [±31.7]), despite small effect sizes (d=0.30). At week 8 and week 12, there was an increase in anxiety scores, 38.7 [±30.8] and 39.2 [±32.9], respectively. Overall decrease of anxiety scores from baseline to endpoint did not find statistical significance (p=0.2114) [15]. Elgawish et al. also analysed anxiety symptoms using the FIQ's anxiety domain [16]. They found a decrease in anxiety scores in all study arms. Patients on local intra-muscular injection therapy showed a reduction of 15.2 [±1.3%] ($p<0.001$). Those on a combination of ozone therapy by local intra-muscular injection and rectal insufflation displayed a greater reduction of 29.4 [±7.3%] ($p<0.001$). However, the control group also obtained a statistically significant reduction in anxiety scores of 14.7[±1.3%] (p=0.03). The authors did not report comparative analysis of anxiety reductions between study arms.

Discussion

Pain is the main symptom of FM and all the articles reported different levels of improvement in the VAS scale. Data related to other associated symptoms were not provided in detail in most articles making it impossible to analysis improvement degree of this symptoms. The route of administration of ozone, dosage and frequency of administration varied between studies and there is insufficient evidence to state which is the best therapeutic protocol. However, Elgawish et al. work, observed a better clinical response in patients who were subjected to rectal insufflation and intramuscular ozone therapy, when compared to the group that only made intramuscular ozone. Hidalgo-Tallón et al. study was the one with the longest follow-up period (12 weeks) and showed a relevant FIQ score improvement only in the first 4 weeks. The remaining works presented approximately 5 weeks as a follow-up time.

Other limitation was the low sample of patients in all studies and also, for the most, there was no control group. On the high side only one study reported adverse effects, in fact Hidalgo-Tallón et al. paper reports adverse effects, such as meteorism following ozone insufflation which was reported by 14 (36.1%) patients. Three (3; 8.1%) patients reported increase in pain and 3 (8.1%) reported constipation. The 3 cases of constipation and the 2 cases of increased pain were long lasting throughout the study period, but none of them led to withdrawal.

Given the lack of studies with a long follow-up period and sufficiently robust samples, further studies are needed to determine prevalence of adverse effects related to ozone therapy in FM treatment. In addition, all studies used different ozone application protocols, so is yet to be determined which is the best route of administration and frequency of treatment as well as concentration and volume of ozone applied.

Limitations: The present rapid review presents several limitations. Firstly, we must consider the inherent limitations of the included studies and its implications. Only 4 articles were included in this review, all with small sample sizes which meant that less than 100 patients received the intervention. Only one study was controlled, and none was randomized. In addition, the assessment of methodological quality revealed critical and serious risk of bias in included studies. As only a few databases were searched, we may have failed to include important studies that may have allowed for a different conclusion to be drawn.

Conclusions

The presence of limitations in all studies and the methodological differences between all the studies make it impossible a proper analysis of ozone use as a non-pharmacological method for FM treatment. At this point we can conclude that there is insufficient evidence to indicate ozone therapy as an effective and safe treatment in the long and / or short-term for FM patients, nevertheless data available are encouraging and should lead to the proposal for new better designed studies to prove effectiveness of ozone therapy in FM.

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