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Ozone Therapy as Add-On Treatment in Fibromyalgia Management by Rectal Insufflation: An Open-Label Pilot Study

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Abstract

Objectives: The objectives of this study were to evaluate the effectiveness and tolerability of ozone therapy by rectal insufflation as add-on therapy in fibromyalgia management.
Design: Patients with fibromyalgia received 24 sessions of ozone therapy during a 12-week period. At each session, the administered dose of ozone was 8 mg (200 mL of gas, at a concentration of 40 μg/mL). Ozone sessions were given 5 days a week during the first 2 weeks, twice a week from weeks 3–6, and weekly from weeks 7–12. Fibromyalgia Impact Questionnaire (FIQ) was the main outcome measure, and was administered at baseline and at weeks 4, 8, and 12. Secondary outcome measures, administered at baseline and at endpoint, were the Pittsburgh Sleep Quality Index, the Beck Depression Inventory, the State and Trait Anxiety Inventory, and the SF-12, the abbreviated form of the Short Form Health Survey. Emergent adverse reactions to treatment were recorded.
Results: FIQ total scores decreased significantly during the study period, with the decrease being observed in the first 4 weeks of the study. Significant improvement was also seen both in depression scores and in the Physical Summary Score of the SF-12. Transient meteorism after ozone therapy sessions was the most frequently reported side-effect.
Conclusions: At the dose and number of sessions used in this study, ozone therapy by rectal insufflation seems to be beneficial for physical symptoms and depression of fibromyalgia.

Introduction

Fibromyalgia is a chronic disorder with a very complex symptomatology. Although generalized pain is considered to be the cardinal symptom of the disease, many other associated symptoms, especially nonrestorative sleep, chronic fatigue, anxiety, and depressive symptoms also play a relevant role in the degree of disability characteristic of the disease.[1] Fibromyalgia pathogenesis is also complex, and both genetic and environmental factors seem to play a role in the pathophysiology of the disease.[2] There is evidence that oxidative stress is increased in fibromyalgia, although it is not known whether this increase is involved as a causative factor in the development of the disease, or whether it is secondary to the patients' unfit condition.[3] In patients with fibromyalgia, increased concentrations of malondialdehyde, and low concentrations of antioxidant enzymes such as catalase, glutathione peroxidase, and superoxide dismutase have been reported by several authors.[4]

Ozone therapy, which is used to treat a wide range of diseases and seems to be particularly useful in the treatment of tissue ischemia and cardiovascular disorders,[5] is thought to act by exerting a mild, transient, and controlled oxidative stress that promotes an upregulation of the antioxidant system and a modulation of the immune system.[6] According to these mechanisms of action, it was hypothesized that ozone therapy could be useful in fibromyalgia management.

The objective of the present study was to get a preliminary evaluation of the potential effectiveness of ozone therapy as add-on treatment in the management of fibromyalgia.

Materials and Methods

The study included adult patients who were diagnosed with fibromyalgia according to the criteria established by the American College of Rheumatology[7] and who were willing to provide written informed consent to participate. Exclusion criteria were pregnant or lactating women, patients with

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hyperthyroidism, and those subjects reporting that they were unable to attend all of the required ozone therapy sessions. Although antioxidant drugs intake was not specifically stated as an exclusion criterion, no patient receiving this kind of treatment at baseline participated in the study.

Ozone was administered as add-on treatment. The ozone generator used was the E80 (Ozonlinea S.L. Bologna, Italy) Plus of Ozonline. Thus, during the 12 weeks of the study duration, patients continued to receive their previous treatment and were asked to maintain this treatment without any change until the end of the ozone therapy.

In each ozone session, the gas was administered rectally in a dose of 8 mg, using a concentration of 40μg/mL and a gas volume of 200 mL. Every patient received a total of 24 sessions, which were distributed as follows: five weekly sessions during the first 2 weeks, two weekly sessions from weeks 3–6, and one weekly session from weeks 7–12.

Doses were selected taking into account other clinical trials using ozone by rectal insufflation.[8–11] Twenty (20) sessions for ozone rectal application have been suggested,[8–11] but in this study the number of treatments was increased up to 24. This treatment scheme was based in the ozone accumulative effect reported by several authors.[12] In the present case, the aim of the study was to evaluate the efficacy of rectal ozone application with a fixed ozone concentration during a 12-week period; this duration of treatment was selected in accordance with the European Medicines Agency recommendations concerning the duration of clinical trials evaluating chronic nociceptive pain drug therapies.[13]

The primary efficacy measure was the Spanish-validated version of the Fibromyalgia Impact Questionnaire (FIQ),[14] which was administered at baseline and at weeks 4, 8, and 12. Additional outcome variables included the Spanish-validated versions of the Beck Depression Inventory (BDI),[15] the Pittsburgh Sleep Quality Index,[16] the State and Trait Anxiety Inventory,[17] and the abbreviated version of the Short-Form Health Survey (SF-12),[18] which were administered only at baseline and at endpoint. Emergent adverse reactions to treatment were recorded at each patient visit.

The intention-to-treat (ITT) sample included those patients who started ozone therapy and had at least one postbaseline evaluation. The analysis of the data of the ITT sample was performed with the last observation carried forward procedure. Significance in the mean changes in the FIQ total scores and Visual Analogue Scale (VAS) subscales of the FIQ were calculated with analysis of variance for paired data; differences between the different visits and baseline were evaluated with the Dunnett's multiple comparison test. Significance in the mean changes between baseline and endpoint of the secondary outcome measures were analyzed with Student's *t*-test for paired data. Effect sizes were calculated according to Cohen's formula and were considered small when lower than 0.5, moderate when between 0.5 and 0.79, and large when ≥ 0.8.

Criteria applied to estimate patients' improvement varied in relation to the evaluated scale according to previous published data. Clinically relevant improvement in fibromyalgia global severity was considered when the decrease of the FIQ total score was $\geq 14\%$ to the baseline value,[19] clinically relevant improvement of pain scores was considered when the decrease in the pain subscale of the FIQ was $\geq 32.5\%$ in relation to the baseline value,[20] and clinically important improvement in depression was considered when the decrease BDI total score was ≥ 5 points.[21]

Results

Thirty-six (36) consecutive patients—33 women and 3 men—were included in the study. Their ages ranged from 22 to 68 years (mean $\pm$ standard deviation [SD]: 50 ± 10), and time from fibromyalgia diagnosis ranged from 0.5 to 33 years (mean $\pm$ SD: 7.4 ± 6.4). All patients but 1 (patient's decision) completed the study period. Comorbidity was common; the most frequent associated pathologies were temporomandibular dysfunction (80.6%), irritable bowel syndrome (55.5%), and migraine (44%). As for pharmacological treatments, 6 (16.7%) patients received no drugs, 14 (38.9%) received one drug, 11 (30.6%) received two drugs, 4 (11.1%) received three drugs, and 1 (2.8%) received four drugs simultaneously. The most frequently prescribed drugs included benzodiazepines (69.4% of subjects), nonsteroidal anti-inflammatory drugs (66.7% of subjects), and antidepressants (47.2% of subjects).

Table 1 shows the evolution of the FIQ total scores and its VAS subscales along the study period. As can be seen, FIQ total scores decreased significantly from week 4 until study endpoint. The improvement particularly affected physical symptoms, such as work impairment, stiffness, pain, fatigue, and morning tiredness, without relevant changes in psychologic symptoms such as anxiety and depression. Ten (27.8%) patients showed clinically relevant improvement in fibromyalgia global severity, and 15 (41.7%) showed clinically relevant decrease in pain scores.

Improvement in physical symptomatology could be also observed in the changes of the secondary outcome variables (Table 2), with a large effect size of -1.08 in the Physical Component Summary of the SF-12 without any modification of the Mental Component Summary. Clinically important decrease of depression scores was observed in 17 (47.2%) patients.

Adverse reactions related with ozone administration were scanty and mild. The most relevant was transitory meteorism following ozone insufflation, which was reported by 13 (36.1%) patients. Three (3; 8.1%) patients reported increase in pain and 3 (8.1%) reported constipation. The 3 cases of constipation and 2 of the increased pain cases were long lasting throughout the study period, but none of them led to withdrawal.

Discussion

To the authors' knowledge, this is the first systematic study evaluating the potential effectiveness of rectal ozone therapy in fibromyalgia, although beneficial effects have been reported after ozone major autohemotherapy in 4 patients with fibromyalgia.[22]

The evolution of the FIQ total score and its subscales (Table 1) shows that the most pronounced improvement was seen in the first 4 weeks of the study, showing a trend to remain unchanged between weeks 4 and 12. This seems likely to be due to the pattern of administration of ozone therapy, given that the maximum frequency of the sessions was during the first 2 weeks and decreased thereafter.

Although the beneficial effects observed with ozone therapy were mostly related to the physical symptoms of fibromyalgia, as could be seen by the number of patients who

Table 1. Mean ± Standard Deviation Values and Effect Sizes of the Fibromyalgia Impact Questionnaire and Its Visual Analogue Scale Subscales During the Study Visits

	Baseline	*Week 4*	*Week 8*	*Week 12*	p
FIQ total score	67.8 ± 18.0	57.7 ± 20.3***	58.8 ± 20.9**	60.3 ± 20.5**	0.0002
		0.57	**0.50**	0.42	
Work impairment	63.9 ± 30.2	42.2 ± 29.3**	32.6 ± 28.6***	44.1 ± 34.9**	< 0.0001
		0.72	**1.04**	**0.65**	
Pain	55.5 ± 35.6	41.2 ± 30.2*	41.2 ± 32.3*	31.6 ± 29.6***	0.0003
		0.65	**0.65**	**0.67**	
Fatigue	55.6 ± 36.7	43.6 ± 33.7	36.2 ± 33.7**	34.8 ± 32.3**	0.0029
		0.33	**0.53**	**0.57**	
Morning tiredness	57.6 ± 35.3	42.1 ± 34.2*	41.3 ± 34.2**	41.1 ± 33.9**	0.0045
		0.45	0.46	0.47	
Stiffness	52.6 ± 35.4	43.6 ± 34.1	33.3 ± 30.7**	29.1 ± 29.5***	< 0.0001
		0.25	**0.54**	**0.66**	
Anxiety	46.2 ± 36.9	34.9 ± 31.7	38.7 ± 30.8	39.2 ± 32.9	0.2114
		0.30	0.20	0.19	
Depression	43.1 ± 34.8	36.8 ± 31.8	33.6 ± 29.8	31.1 ± 30.2	0.1720
		0.18	0.27	0.34	

*$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$ in relation to baseline. Bold numbers indicate moderate or large effect sizes.
FIQ, Fibromyalgia Impact Questionnaire; VAS, Visual Analogue Scale.

showed clinically relevant improvement in fibromyalgia global severity and pain scores, it is interesting to realize that depression was also markedly improved in 47% of patients. If this was just a reflection of the improvement in the general well-being or if it was a specific effect due to ozone treatment is a question that the design of this study cannot answer, but which would be interesting to address in further trials, since the potential effects of ozone therapy on mental health have not yet been studied.

Multiple factors and mechanisms are involved in the pathogenesis of fibromyalgia.[2] Oxidative stress and nitric oxide may play an important role in fibromyalgia pathophysiology; however, it is still not clear whether oxidative stress abnormalities are the cause or the effect of the disease.[3] Nitric oxide promotes the exaggerated release of excitatory amino acids and substance P from presynaptic afferent terminals and causes the dorsal horn to become hyperexcitable.[23] It seems likely that nitric oxide/peroxynitrite pathways play an important role in pain processing in the spinal cord.[24] On the other hand, increased intracellular Ca^{2+} evokes K^+ efflux from the sarcomere and subsequent increase in sensitization of muscle nociceptors, thereby resulting in pain and other related findings such as muscle weakness, fatigue, and stiffness.[25] Chung et al. suggest that oxidative stress may be more prominent in patients within the fibromyalgia spectrum of disorders in which fatigue is more prominent.[26] There is evidence that patients with fibromyalgia have alterations in muscle metabolism and structure indicative of oxygenation and/or oxidative system abnormalities. These structural damages may contribute to poor oxygen diffusion, decreased oxidative phosphorylation, and reduced ATP synthesis, which may further increase oxidative stress and peroxidation of membrane lipids.[3] The role of free radical–mediated oxidative damage in the etiopathogenesis of fibromyalgia has been investigated,[27–30] and recent studies have confirmed the oxidative stress background of this disease due to a defect in the distribution and metabolism of coenzyme Q10 in cells and tissues.[31,32] Deficiency of coenzyme Q10 (an essential electron carrier in the mitochondrial respiratory chain and a strong antioxidant) alters mitochondria function and mitochondrial respiratory complexes organization and leading to increased reactive oxidative species (ROS) generation. Also, cytokines (tumor necrosis factor α, interleukin [IL]-1, interleukin-6, and interleukin-8) are considered to play a role in the pathogenesis and clinical manifestations of fibromyalgia. On the basis of these findings, Wallace et al.[33] hypothesized that IL-8 and IL-6 may play a role in modulating fibromyalgia symptoms, since IL-8 promotes sympathetic pain and IL-6 induces hyperalgesia, fatigue, and depression.

It has been already demonstrated that some of the therapeutic effects of ozone therapy could be related to the fibromyalgia-related pathophysiologic mechanisms cited above. The homeostasis redox, as well as the nitric oxide,

Table 2. Mean ± Standard Deviation Values and Effect Sizes of the Secondary Outcome Variables

	Baseline	*Endpoint*	p
BDI	23.1 ± 10.5	18.4 ± 9.1	0.0002
		0.45	
PSQI	14.4 ± 3.8	12.8 ± 4.5	0.0209
		0.42	
State anxiety	37.1 ± 11.9	33.2. ± 12.1	0.0284
		0.33	
Trait anxiety	36.4 ± 11.7	32.6 ± 11.0	0.0047
		0.32	
SF-12 PCS[a]	27.3 ± 5.8	33.6 ± 8.9	0.0012
		−1.08	
SF-12 MCS[b]	33.3 ± 12.7	37.2 ± 13.0	0.1241

[a]Physical Component Summary and [b]Mental Component Summary; in the SF-12 higher values indicate improvement. Bold number indicates large effect size.

BDI, Beck Depression Inventory; PSQI, Pittsburgh Sleep Quality Index; SF-12 PCS, Short-Form Health Survey Physical Component Summary; MCS, Mental Component Summary.

calcium, and cytokine homeostasis achieved with the ozone treatment, and the improvement in oxygen metabolism have been proven in preclinical and clinical studies.[8,10,34–39] Superoxide dismutase–manganese dependence located in mitochondria is increased after the ozone treatment in the model of liver ischemia–reperfusion preserving mitochondrial function and cellular redox balance.[40] Recent studies have demonstrated that ozone therapy was able to reestablish cellular redox balance after 2 weeks of ethanol withdrawal in Lewis rats. In those studies, an improvement of behaviors such as memory/learning, locomotor activity, and anxiety decrease was observed. The beneficial effects of ozone on different behaviors associated with ethanol withdrawal syndrome indicate that important neurotransmitter systems are new therapeutic targets.[41] Therefore, ozone, through mechanisms that promote a regulation of endogenous nitric oxide concentrations, the maintenance of an adequate cellular redox balance, and improvement in oxygen diffusion, could justify the beneficial effects achieved in patients with fibromyalgia.

The most common method of ozone administration in the treatment of systemic diseases is major autohemotherapy.[5] This is, however, an invasive procedure, and pain in the site of injection and ecchymosis are frequent, even if mild, side-effects, although infrequently, phlebitis and blood extravasation may also occur. Additionally, to maintain its efficacy in chronic diseases, ozone needs to be administered repeatedly during the treatment period, a situation in which intravenous injection is not the ideal method of drug administration. Rectal insufflation of the gas is a suitable administration alternative even if, as shown in a recent published article concerning the treatment of asthma,[8] it is less efficient than major autohemotherapy.

Adverse reactions were mild and mostly transient, a fact that contributes to support the steadily growing idea that ozone therapy is usually a well-tolerated treatment. Meteorism, lasting 1–2 days after ozone sessions, was the most common side-effect, probably due to the 200 mL of gas delivered, and its intensity decreased as the intervals between sessions become longer. However, a lower gas volume (at a higher concentration of ozone, in order to maintain the same quantity) could have increased the irritating potential of ozone on the rectal mucosa.

The main limitation of this study is its noncontrolled design. This study, however, was conceived as preliminary research aiming to evaluate the potential usefulness of ozone therapy by rectal insufflation in patients with fibromyalgia. Nevertheless, the finding that fibromyalgia physical symptoms were those showing greater improvement is a fact that argues against a possible placebo effect despite the lack of a control group.

Additional limitations are the dose and timing of ozone administration. As there are no published studies concerning rectal ozone therapy in fibromyalgia, the current study needed to extrapolate both the dose of ozone and the duration of the therapy from data coming from other studies.[8–11] Borrelli and Bocci[22] reported significant improvement in 4 of 5 patients with fibromyalgia receiving ozone major autohemotherapy administered twice a week in a dose of 2 mg during the first 2 weeks and 4 mg in the remaining sessions, which ranged from 24 to 36 sessions. Because it is known that the efficacy of rectal ozone therapy is lower than that of major autohemotherapy,[8] it was decided to administer a concentration of 40 mg/L with a volume of 200 mL (dose of 8 mg) per session. However, because rectal insufflation is easier to perform than major autohemotherapy, and taking into account that the ozone effect is accumulative, it was decided to administer a greater number of sessions in the first weeks of the study in order to obtain a quicker clinical response and to lengthen progressively the sessions to maintain the initial response and to avoid excessive disturbance to the patient's life. The antioxidant defense system begins to be stimulated between the fifth and tenth ozone application with the corresponding ozone therapeutic effects.[12] Thus, it was an empirical and pragmatic approach, and additional models of treatment should be explored in future studies in order to investigate whether more intensive ozone sessions during the first week of treatment cause a greater level of improvement in fibromyalgia symptomatology or whether it is necessary to increase the number of sessions.

Conclusions

In conclusion, at the dose and number of sessions used in this study, ozone therapy by rectal insufflation seems to be beneficial mainly for the physical symptoms of fibromyalgia, though anxiety and depression also improved. The current results suggest that further evaluation of ozone therapy in fibromyalgia, if possible with a controlled design, will be worth performing. It seems especially important to investigate the optimum ozone dosage, number of weekly sessions, and length of treatment cycle required to obtain maximum therapeutic benefit.

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Disclosure Statement

No competing financial interests exist.

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