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## RESEARCH ARTICLE

## OZONE AS AN ADJUVANT THERAPY IN TREATMENT OF FIBROMYALGIA SYNDROME

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### Abstract

**Background:** Fibromyalgia syndrome (FMS) is characterized by an increase in pain perception in the central nervous system, whose main symptom is chronic widespread pain at muscles, tendons and ligaments but not in joints, accompanied by symptoms that disrupt the daily living activities of the patients.

**Objective of** this study was to assess the effectiveness of ozone therapy either by local intra-muscular injection or combined local intra-muscular injection and rectal insufflation as an adjuvant therapy in FMS.

**Patients & Methods:** Fifty patients with FMS were recruited for this study and classified into three treatment groups .Group (A),20 patients treated with local intra-muscular ozone injection 2 sessions /week for 5 weeks. Group (B),20 patients treated with local IM injection in tender points and rectal ozone therapy /twice weekly for 5 weeks and the third group (C),include10 patients were the control group not receiving ozone therapy .Assessment were done by visual analogue scale (VAS) for pain , fibromyalgia impact questionnaire (FIQ), Hamilton depression rating scale (HDRS) and Short form 12 – Items health survey (SF-12)for depression , sleep disturbance and daily living activity assessment at baseline and 5weeks later after ozone treatment .

**Results:** 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 %. The improvement was mainly in physical symptoms, such as work impairment, stiffness, pain, fatigue, and morning tiredness. There were significant differences in scores of HDRS and SF – 12 items between the baseline and after 5 weeks of ozone treatment in both groups (A & B) than in control group(C). Significant reduction in VAS by 35.3 % in group A and 45.3 % in group B after treatment while in group C 17.7 %.

**Conclusion:** ozone therapy given by rectal insufflation together with local tender point's injection seems to be beneficial than local tender point's injection alone, mainly for the physical symptoms of FMS, though anxiety and depression also improved. The ozone therapy can be considered as an interesting adjuvant therapy in treating symptoms of FMS.

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## INTRODUCTION

Fibromyalgia is a medical condition characterized by a chronic widespread pain and a heightened and painful response to pressure (Ngian G et al 2011) .Fibromyalgia symptoms are not restricted to pain, leading to the use of

the alternative term fibromyalgia syndrome (FMS) for the condition. Other symptoms include debilitating fatigue, sleep disturbance, and joint stiffness (Wolfe 1989). Some people also report difficulty with swallowing (Wallace and Hallegua 2002), bowel and bladder abnormalities (Clauw et al 1997) numbness and tingling (Simms and Goldenberg 1988) and cognitive dysfunction (Glass 2006). Fibromyalgia is frequently associated with psychiatric conditions such as depression and anxiety and stress-related disorders such as post-traumatic stress disorder (Buskila and Cohen 2007) and (Sweinhart et al 2008). Not all people with fibromyalgia experience all associated symptoms (Yunus 1983). Fibromyalgia is estimated to affect 2–8% of the population (Clauw 2014), with a female to male incidence ratio that is somewhere between 7:1 and 9:1 (Bartels et al 2009) and (Hawkins 2013). New diagnostic criteria were developed by the **American College of Rheumatology (ACR) (Wolfe et al 2010)**. The new criteria introduce the associated symptomatology as an additional criterion for the diagnosis. Therefore, it is not surprising that many authors have looked into the relationships between pain and associated comorbidities, such as functional limitations, anxiety and depression (Cecilia et al 2015). Accordingly, patients consider that the widespread pain and intense fatigue they feel are responsible for their limitations or the disabilities they suffer in their daily lives (Rivera 2012).

The cause of fibromyalgia is unknown. However, several hypotheses have been developed including "central sensitization. A sensitization effect that occurs in certain neurons leading to the establishment of fibromyalgia and sometimes a mood disorder (Maletic and Raison 2009). There is evidence that genetic factors may play a role in the development of FMS, as there is a high aggregation of fibromyalgia in families (Arnold et al 2004).

The association between pain, anxiety and depression has been extensively explored in previous literature on chronic pain, establishing a bidirectional relationship that explains the vicious circles of pain–anxiety/depression (Woo 2012). Some neurochemical abnormalities that occur in FMS also regulate mood, sleep and energy, thus explaining why mood, sleep and fatigue problems are commonly co-morbid with fibromyalgia (Clauw et al 2011).

There is no definitive cure for FMS and worse people evolve no exercise, take many medications, have psychiatric disorder and unmotivated patients (Fernandez et al 2007). Treatment by providing medicines to improve pain and sleep, make gradual exercise, teach them to have proper management of breath, psychological treatment and antioxidants (Grandos et al 2008).

Ozone (O<sub>3</sub>), a gas discovered in the mid-nineteenth century, is a molecule consisting of three atoms of oxygen in a dynamically unstable structure. The gas is colorless, acrid in odor and explosive in liquid or solid form. It has a half-life of 40 min at 20°C and about 140 min at 0°C. Its basic function is to protect humans from harmful effects of UV radiation (Dipaolo et al 2004).

The medical use of ozone was initiated in the 19th century and multiple therapeutic effects in wound healing were found due to the property of releasing nascent oxygen, which has been shown to have bactericidal capabilities and to stimulate antioxidant enzymes (Agrillo et al 2012). Ozone therapy has been successfully used in treatment of patients with lumbar disc herniation, it has been found to be helpful in reducing pain after failure of other conservative treatments, intra-muscular paravertebral infiltration is now the technique mainly used as it is much less invasive (Paoloni et al 2009). Intra-articular O<sub>3</sub> therapy for pain control in osteoarthritis (OA) of the knee, Ozone is being currently tested for its effectiveness in relieving the pain in patients with OA of the knee (intraarticular ozone cited 2010).

Several mechanisms of action have been proposed to explain the efficacy of ozone therapy including analgesic, anti-inflammatory and oxidant action on proteoglycans. Ozone is administered in the form of an oxygen-ozone gas mixture using various percutaneous methods (Booci 2006).

## OBJECTIVE

Is to assess the role of ozone therapy given either by local intra-muscular injection or combined local intra-muscular injection and rectal insufflation in improving the patients' symptoms of FMS including pain, depression, sleep disturbances and daily living activities.

## PATIENTS AND METHODS

Fifty patients with primary FMS diagnosed according to the ACR criteria [13], were recruited for this study from the outpatient clinic and inpatient department of Rheumatology and Rehabilitation and from outpatient clinic of Psychiatric department, Zagazig University Hospitals. All patients included in the study were females. Their ages ranged from 28 to 56 years. They were classified into three treatment groups: **Group (A)**, includes 20 patients treated with local intra-muscular ozone injection in tender points 2 sessions /week for 5 weeks at a concentration of 15 µg/mL with volume 10 to 20 ml of gas injected in about 7 – 13 tender points per session.

**Group (B)**, includes 20 patients treated with local 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 per session. And rectal insufflations of ozone at a concentration of 50 µg/mL with volume up to 200 mL, 2 sessions / weekly for 5 weeks and the **third group (C)** was the control group that includes 10 patients not receiving ozone therapy.

During the 5 weeks of the treatment duration, patients continued to receive their previous medical treatment and were asked to maintain this treatment without any change until the end of the ozone therapy. The study was approved by the Ethics Committee of the university and the patients were included in the study after giving their informed consent after explanation of the purpose and procedures of the study.

**Exclusion criteria:**

Pregnant or lactating women, diabetic, hepatic, cardiac or renal patients were excluded. Patients with secondary FMS and patients with hyperthyroidism also excluded.

**All patients were subjected to:**

- Complete history taking including the duration of disease, drug therapy, articular and other non-articular manifestations including fatigue, sleep disturbances, cognitive dysfunction and depression or anxiety.
- Complete general and musculoskeletal examinations.
- Local examination of tender and control points.
- Laboratory investigations mainly to exclude secondary FMS, including (CBC, ESR, CRP, RF, Serum uric acid, Liver & Renal function tests).

**Clinical Assessment:**

**1- Visual Analog Scale (VAS)** 0-100 mm for pain assessment.

**2- Fibromyalgia Impact Questionnaire (FIQ):** The FIQ is an instrument designed to measure the overall impact of fibromyalgia over many dimensions (**Buckhardt et al 1991**). The FIQ is composed of 10 items. The first item contains 11 questions related to physical functioning – each question is rated on a 4 point Likert type scale. Items 2 and 3 ask the patient to mark the number of days they felt well and the number of days they were unable to work (including housework) because of fibromyalgia symptoms. Items 4 through 10 are horizontal linear scales marked in 10 increments on which the patient rates work difficulty, pain, fatigue, morning tiredness, stiffness, anxiety and depression. Its scores range from 0 to 100, with 100 marking the worst case.

**3- Short form 12 – Items health survey:** Is a 12 – items questionnaire that can be used to measure physical and mental health (**Ware et al 1996**). The instrument produces two summary scores, the physical component summary (PCS) and the mental health component summary (MCS). It is widely used as a short measure of health status in social surveys, studies investigating the impact of specific disease upon patients and treatment trials (**Jenkinson et al 1997**). The measure includes 12-questions including a global question of perceived health status, to which respondents indicate whether they think their overall health is excellent, very good, good, fair or poor. The scores are represented as t-scores that are linear transformations with a mean of 50 and a standard deviation of 10.

**4- Hamilton depression rating scale (HDRS):**

A rating scale is described for use in assessing the symptoms of patients diagnosed as suffering from depressive states. The scale contains 21 variables. The variables are measured either on five-point (0 – 4) or three-point scales (0 – 2), the latter being used where quantification of the variable is either difficult or impossible (**Hamilton 1960**). A score of 0–7 is normal, 8–13 is mild depression, 14–18 moderate depression, 19–22 severe depression and ≥23 very severe depression and a score of ≤7 indicates remission of symptoms (**Lecrabier 2002**).

**Administration of ozone therapy:**

**Ozone was generated by using HYRER MEDOZON apparatus (HAB) HERRMAN.**

**1-Rectal ozone therapy:** The ozone by rectal insufflation was given to group B only, In each ozone session, the gas was given rectally by infusing the gas slowly through a plastic catheter that was introduced through the anus into the rectum by using lubricant gel and then the gas was given by a 50 ml syringe at the distal end of the catheter slowly over 1 to 2 minute using a concentration of 50µg/mL and a gas volume up to 200mL. Every patient received 2 sessions per week for 5 weeks.

All patients informed to evacuate the rectum before session and after session prevent gas leakage for 30 minutes to ensure good absorption

**2-local ozone therapy:** Intra-muscular ozone injection in the tender points given to both group A and group B. In each ozone session it was given at a concentration of 15 µg/mL, up to 40 mL volume in the session with injection of about 3 ml of gas in each point, about 7 – 13 points were injected per session Local ozone therapy was given 2 sessions weekly for 5 weeks for both groups.

**Statistical analyses** The collected data were coded and analyzed using SPSS VERSION 16.0. For quantitative data mean, standard deviation, percentage of change (new-actual)/actual, paired t test, and ANOVA (analysis of variance). The level of significant  $p < 0.05$ , the power of study 80% and the confidence interval 95%.

## RESULTS

Fifty female patients with primary FMS were included in this study, Their ages ranged from 28 to 56 years and the time from fibromyalgia diagnosis ranged from 0.5 to 3 years. About pharmacological treatments all patients received 2 types of treatment. The prescribed drugs included amitriptyline 25 mg per day .

**Table (1)** shows the general characteristics of all patients in the 3 groups at baseline with no statistical significant differences between them.

In group A that received local IM ozone injection in tender points there is statistically significant difference in values and percent changes of all clinical parameters of evaluation ( FIQ total score, VAS), SF-12 Items and HDRS between base line and 5 weeks after treatment this is shown in **Table (2)**

In group B that received rectal insufflations and local IM ozone injection in tender points there is statistically significant difference in values and percent changes of all clinical parameters of evaluation ( FIQ total score, VAS), SF-12 Items and HDRS between base line and 5 weeks after treatment this is shown in **Table (3)**

While after 5 weeks of follow up the changes in all scores and percent changes in control group (C) that did not receive ozone therapy showed statistical significant differences but not of all parameters as in the other two groups (A&B) shown in **Table (4)**.

**Table (5)** shows statistically significant differences between all clinical parameters of evaluation ( FIQ total score, VAS), SF-12 Items and HDRS in the three groups after 5 weeks of treatment by ozone with the highest changes with group B followed by group A and the lowest changes were in group C

**Table (1) : General characteristics of all groups at baseline :**

	Group A	Group B	Group C	F	P- Value
AGE/years	47.5±4.8	45.6±4.2	45.2±3.9	0.40	0.87
Disease duration/years	1.5±1.6	1.9±1.1	1.6±1.3	0.67	0.53
BMI	26.5±2.7	26.6±2.4	26.0±2.7	0.08	0.93
VAS	66.6±5.9	66.8±5.2	68.1±4.3	0.02	0.99
FIQ total score	86.9±11.1	89.5±15.2	89.2±12.4	0.07	0.99
HDRS	12.6±4.4	13.3±2.2	12.9±1.7	0.09	0.97
SF 12-Items	21.3±4.5	21.9±5.3	22.3±4.9	0.04	0.97

BMI= Body mass index , VAS= Visual analogue scale , HDRS= Hamilton depression rating scale , SF – 12 items= Short form -12 items.

**Table (2) :Differences in all scores and percent changes in group (A) between baseline and after 5 weeks treatment :**

	Baseline	After 5 weeks	% of change	P – Value
FIQ Total score	86.9 ± 11.1	53.7 ± 7.3	33.4 ± 9.7%	0.00
Work difficulty	62.8 ± 4.1	38 ± 9.6	36.9 ± 14.3%	0.00
Pain	55.5 ± 5.0	26.3 ± 4.5	36.1 ± 3.7%	0.00
Fatigue	58.4 ± 3.6	48.1 ± 3.7	14.7 ± 2.4%	0.00
Morning tiredness	53.3 ± 4.1	42.3 ± 4.0	22.4 ± 2.7 %	0.00
Stiffness	60.3 ± 3.5	51.7 ± 2.8	14.3 ± 1.2%	0.00
Anxiety	45.7 ± 3.1	39.7 ± 3.1	15.2 ± 1.3%	0.00
Depression	44.7 ± 3.5	39.5 ± 2.1	15.7 ± 1.3%	0.00
SF-12 Items	21.3±4.5	29.8±3.1	6.7 ± 1.9%	0.00
VAS	66.6±5.9	32.3±6.3	35.3± 5.1%	0.00
HDRS	12.6 ± 1.4	9.2± 0.8	3.1± 0.4%	0.04

**Table (3): Differences in all scores and percent changes in Group (B) between baseline and after treatment:**

	Baseline	After 5 weeks	% of change	P – Value
<b>FIQ Total score</b>	89.5 ± 15.2	46.4 ± 5.2	47.7 ± 10.9 %	0.00
<b>Work difficulty</b>	65.5 ± 5.1	35.5 ± 5.1	46.1 ± 3.7 %	0.00
<b>Pain</b>	57.1 ± 4.0	21.5 ± 3.7	39.6 ± 9.1 %	0.00
<b>Fatigue</b>	55.7 ± 3.1	45.6 ± 2.4	19.1 ± 1.1 %	0.00
<b>Morning tiredness</b>	53.4 ± 4.7	39.4 ± 4.7	28.4 ± 2.4 %	0.00
<b>Stiffness</b>	63 ± 4.6	48.1 ± 4.7	29.1 ± 2.8 %	0.00
<b>Anxiety</b>	46.6 ± 3.1	30.7 ± 3.4	29.4 ± 7.3 %	0.00
<b>Depression</b>	45.3 ± 5.0	36.3 ± 5.0	20.0 ± 2.3 %	0.00
<b>SF-12 Items</b>	27.9 ± 5.3	34.6 ± 6.1	8.1 ± 2.2%	0.00
<b>VAS</b>	66.6 ± 5.9	22.3 ± 7.3	45.3± 9.1%	0.00
<b>HDRS</b>	13.3 ± 2.2	7.4 ± 0.8	5.7± 1.4%	0.00

**Table (4): Differences in all scores and percent changes in Group (C) between baseline and after 5 weeks:**

	Baseline	After 5 weeks	% of change	P – Value
<b>FIQ Total score</b>	89.2 ± 12.4	65.3 ± 6.0	17.3 ± 10.4 %	0.00*
<b>Work difficulty</b>	62.3 ± 3.5	55.6 ± 3.5	9.3 ± 1.1%	0.06
<b>Pain</b>	57.7 ± 4.5	47.7 ± 4.5	17.4 ± 1.4 %	0.00*
<b>Fatigue</b>	57.4 ± 5.2	53.7 ± 9.1	11.4 ± 7.7 %	0.05
<b>Morning tiredness</b>	53.6 ± 4.5	46.3 ± 4.05	13.2 ± 5.1 %	0.00*
<b>Stiffness</b>	62 ± 4.6	56 ± 4.6	9.7 ± 0.7 %	0.00*
<b>Anxiety</b>	47 ± 4.0	41.2 ± 4.0	14.7 ± 1.3 %	0.03*
<b>Depression</b>	47.3 ± 4.5	40.3 ± 3.5	14.7 ± 0.7 %	0.00*
<b>SF-12 Items</b>	22.3 ± 4.9	28.4 ± 2.9	3.9±0.8%	0.03*
<b>VAS</b>	68.1 ± 4.3	41.7 ± 3.8	17.7± 1.4%	0.04*
<b>HDRS</b>	12.9 ± 1.7	10.5 ± 0.6	2.7± 0.3%	0.04*

**Table (5) :Comparison between all groups as regard the total scores of FIQ, SF – 12 Items, VAS and HDRS after 5 weeks:**

	Group(A)	Group (B)	Group(C)	P - off test
<b>FIQ Total score</b>	33.4 ± 9.7%	47.7 ± 10.9 %	17.3 ± 10.4 %	0.00*
<b>SF-12 Items</b>	6.7 ± 1.9%	8.1 ± 2.2%	3.9±0.8%	0.00*
<b>VAS</b>	35.3± 5.1%	45.3± 9.1%	17.7± 1.4%	0.00*
<b>HDRS</b>	3.1± 0.4	5.7± 1.4	2.7± 0.3	0.00*

## DISCUSSION

Despite the extensive efforts to delineate an effective treatment in the last four decades, FMS continues to be a very difficult chronic pain condition to treat, particularly for non-pharmacologic approaches. A large variety of modalities have been tested for treating FMS. Overall, no single modality has been found to be universally effective for all FMS patients, or all FMS symptoms in an individual patient (Okifuja 2013). The objectives of this study were to evaluate the effectiveness of ozone therapy given either by local intra-muscular injection or by local and systemic by rectal insufflation in FMS management. We found that the combined local and rectal ozone therapy given to group (B) showed decreased FIQ total scores significantly with 47.7 % improvement after 5 weeks of treatment with statistical significant differences with the control group (C) showed improvement of 17.3 %. And group (A) showed improvement of 33.4 % after 5 weeks of treatment with local intra-muscular ozone therapy. The improvement particularly affected the physical symptoms, such as work impairment, stiffness, pain, fatigue, and morning tiredness. Significant reduction in VAS after treatment especially in group (B) with improvement of 45.3 % compared with control group (C) 17.7 % and 35.3 % in group (A). It is interesting to realize that depression was also markedly improved in both group (A and B) of patients with significant

differences in scores of HDRS and SF – 12 items between the baseline and after 5 weeks of ozone treatment in both group. If this was just a reflection of the improvement in pain and 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. All these results were in agreement with a study done by **Hidalgo-Tallo'n et al;(2013)**,]That evaluated the effectiveness and tolerability of ozone therapy by rectal insufflation as add-on therapy in FMS. Patients received 24 sessions of ozone therapy during a 12-week period. At each session, the administered dose of ozone was 200mL of gas, at a concentration of 40ug/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.The FIQ was the main outcome measure and was administered at baseline and at weeks 4, 8, and 12. Secondary outcome measure was the short form health survey SF- 12, They reported that 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. They concluded that ozone therapy by rectal insufflation seems to be beneficial for physical symptoms and depression of fibromyalgia.

**LongasVélez,(2014)**Studied the impact of ozone therapy in improving patients' pain and daily activities to give them a better quality of life . Clinical experience is described using ozone therapy in 30 women diagnosed with FMS. Patients were treated with O<sub>2</sub>-O<sub>3</sub> intramuscular with 10 sessions 2 times a week at doses of 15 µg/mL, together with systemically 10 sessions 2 times a week alternating rectal insufflation and intravenous administration of saline 0.9% ozonated. The outcome of patients was continued by monitoring clinical symptoms and evaluation of the VAS. The results showed an improvement in pain with 33% VAS 3-4 in the second week, improved sleep disorder in 46.6%, mood and daily activities by 40% and appreciated a decrease in the amount of drugs consumed by 30% of patients. The ozone therapy can be considered as an interesting as adjuvant therapy in the symptoms of fibromyalgia.

This is the first study that comparing the effect of rectal and local ozone versus local ozone alone as an adjuvant therapy in treatment of FM.

The limitations of this study were, the short duration of treatment, small number of patients and extended period for follow up is needed to determine if the ozone has long term or short term effect on FMS patients.

**Recommendations** :There were only very few numbers of studies that discussing the same issue of our study so we recommend other studies with different designs to explain if the improvement of physical activity or depression is due to improvement of pain or the effect of ozone itself.

**There were no conflicts of interest between authors.**

## Conclusions

In conclusion, ozone therapy given by rectal insufflation together with local intramuscular tender point's injection seems to be beneficial than local intramuscular injection of tender points alone in improving the physical symptoms of FMS, though anxiety and depression also improved. Ozone therapy acts as an interesting adjuvant therapy in treatment of symptoms of FMS.

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