

Fibromyalgia treated with oxygen-ozone auto-haemotherapy (O₂-O₃-AHT): a case study on 200 patients with a modified 10-PI-NRS evaluation

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Abstract. – OBJECTIVE: Fibromyalgia (FM) is a concerning chronic disease showing as widespread pain, muscle stiffness, sleep disturbances, chronic fatigue, and depressed mood, for which no sound therapy is yet available to date. In this article we assessed a wider patients' cohort the efficacy of oxygen-ozone auto-hemotherapy (O₂-O₃-AHT) previously reported.

PATIENTS AND METHODS: A number of 200 FM-patients accessed the study and were treated with 3-4 runs of O₂-O₃-AHT, following their signed consent. A modified 10 points-PI-NRS were used to evaluate pain intensity before and after the conclusion of the complete ozone-treatment cycle (1 month). Kruskal-Wallis' test and other statistics were used at $p < 0.05$ level of significance.

RESULTS: A quite complete rehabilitation of the musculoskeletal function and of the overall arthralgia was observed in 76% of the patients at one month of follow-up. The number of patients having a reduction in the PI-NRS score from 10 (the maximal observed) to 3 (including 10-1 and 10-2) following only two runs of O₂-O₃-AHT was 23.5%, whereas only 17.5% did not show any significant improvement ($\Delta_{PI-NRS} = 0$ or 1), so assessing that the efficacy of O₂-O₃-AHT, independently from ages, encompassed at least 41% in a moderate way and 64.5% of the treated patients, as a whole.

CONCLUSIONS: Oxygen-ozone autohemotherapy represents a formidable therapeutic approach for FM, deserving further studies to be made in order to fully elucidate ozone effect of this pathology.

Key Words:

O₂-O₃-AHT, Fibromyalgia, Oxygen-ozone autohemotherapy, Ozone.

Introduction

Fibromyalgia (FM) is a chronic disease characterized by widespread pain, muscle stiffness,

sleep disturbances, chronic fatigue, and depressed mood^{1,2}. It can compromise the performance of common daily activities, as well as having a negative impact on most aspects related to the quality of life. In Italy, it affects almost 2 million Italians and usually occurs between the ages of 25 and 55. Women are more likely to develop fibromyalgia than men³.

In 1990, the American College of Rheumatology (ACR) established the presence of pain spread throughout the body and soreness in at least 11 of 18 points, the so-called tender points or "points of tenderness"⁴, as symptoms characterizing FM. In 2010, the ACR itself redefined these criteria⁵. In addition to this, other new factors began to be considered as key features of fibromyalgia, such as: extreme sensitivity to pain, fatigue, muscle stiffness, dysfunction of the autonomic nervous system, irritable bowel syndrome, dry mouth, loss of the biological clock that causes insomnia, fatigue and dizziness.

This complex panoply of symptoms suggests that FM etiopathogenesis is still far from being fully elucidated. Chronic pain is the major hallmark, but its causes remain undefined. A neurophysiological hypothesis suggests that FM may be caused by cortical hyperfunction ultimately eliciting a peripheral small afferent damage³, yet no typical laboratory marker allows to diagnose FM *per se*, aside from a clinical assessment, which stands as the only approach to earn a diagnosis of FM⁶. As the major etiopathogenetic causes are not known, there is currently no sound and reliable therapy for fibromyalgia, but several therapies are yet available that tend to control and alleviate symptoms, and possibly affect the disorder. Our recent experience with the use of ma-

major oxygen-ozone autohemotherapy⁷, where about 65 patients suffering from FM were treated and resulted in a preliminary significant improvement (>50% of symptoms) in 45 patients (70%), without important side effects, encouraged our research crew to update the recent evidence previously reported on patients treated from February 2016 to October 2018⁷ and, with the aid of the international Scientific Society of Oxygen Ozone Therapy (SIOOT), assessing our previous results with a wider FM patients' cohort. The medical attempt to try novel approaches able to address FM is crucial to restore health, comfort and wellbeing in patients who suffer from a debilitating chronic ailment able to reduce people's social activity and interaction.

In this paper, we report an experimental and clinical study on the use of O₂-O₃-AHT in patients with fibromyalgia, in order to assess the therapeutic use of ozone in this pathology.

Patients and Methods

Patients

A number of 216 outpatients of the Tirelli's Clinical Group, in Pordenone (Italy), were enrolled in the study, after having thoroughly read, approved and signed an informed consent about the use of data for research purposes, according to the Ethical approvals of the Italian Society of Oxygen-Ozone Therapy (SIOOT), in compliance with the Helsinki Declaration. Twelve patients left the research study for various personal and health reasons, four patients were excluded because of limitations in the planned analyses. Inclusive criteria were represented by a confirmed diagnosis of fibromyalgia (FM), based on the positivity of all tender points, on the EULAR revised Recommendations for the Management of Fibromyalgia, and on the recent evidence and standardization, with evidence of painful symptoms and debilitation⁸⁻¹¹. Exclusive criteria were the presence of multiple sclerosis or rheumatoid arthritis. The 200 patients included in the study were mostly females (82.5%), with mean ages of 44.68 ±11.91 SD (females) and 43.80 ±9.30 SD (males) ($p = 0.28914$).

Patients' Treatment with O₂-O₃-AHT

FM patients were treated from three to four sessions of major autohemotherapy with oxygen-ozone (O₂-O₃-AHT), following the standardized criteria from the Italian Society of Oxygen-Ozone Therapy (SIOOT). Patients underwent

not less than two weekly sessions of major oxygen-ozone autohemotherapy, according to the protocol previously assessed by the Italian Society of Oxygen-Ozone Therapy (SIOOT)¹².

Treatment lasted 30 minutes for each session and despite evident improvements did not occur before one week following the O₂-O₃-AHT, pain relief and a global amelioration of the painful regions of the body were much more lasting than with any pharmaceutical treatment.

Patients underwent 200 ml venipuncture peripheral blood withdrawal and samples were collected in a CE certified SANO3 bag, then immediately subjected to 45 µg/mL of ozone in a O₂-O₃ mixture, which was continuously monitored and dosage-regulated by the instrumental device Multioxygen Medical 95 CPS (Gorle, BG, Italy). This was disposed in the form of an outpatient unit for O₂-O₃ therapy, and allowed physicians standing close the patient's bed to customize the gas mixture according to the therapy request. In this perspective, the O₂-O₃ mixture generator was regulated by a proper microprocessor ensuring the ozone delivery with the highest precision requested, once the O₃-O₂ mixture and ozone amount was selected by the operator. This allowed the customization of the treatment *via* selecting the O₃ dosage in a continuous range, i.e., from 1 to 100 µg of O₃. When correctly adjusted, the 200 mL of ozonized blood was promptly reintroduced into the patient's circulatory blood, directly from the sterile bag.

The therapy method of O₂-O₃-AHT required therefore an ozone generator, medical grade oxygen, a sterile syringe and a certified bag endowed with an intravenous cannula.

In the case that after three weeks from the O₂-O₃-AHT treatment, the PI-NRS delta score was null, a fourth session of O₂-O₃-AHT was performed, using 150 mL treated blood at 45 µg/mL of ozone in a O₂-O₃ mixture. An overall median of 157 mL, CI₉₅ = 138-296 mL of blood was ozonized and then reintroduced for each treated patient^{7,12,13}. Patients were followed up to 30 days following the second O₂-O₃-AHT session and asked to complete the PI-NRS questionnaire, as previously agreed.

Patients' Evaluation with the Modified 10 Scores-PI-NRS

A modified 10-points Pain Intensity-Numerical Rating Scale (10-PI-NRS) has been used in this research study, on the basis of recent statistical comparisons with the 11-PI-NRS¹⁴. Previous reports¹⁵ had raised the need to use a 10-points (0 = no pain and 10 = worst possible pain) PI-NRS

instead of a 11-points score, in order to make the evaluation of a rank as a decimal scale easier.

The patient indicated the intensity of the pain verbally or by drawing a circle on the number that best describes it. The same operation was held by two independent researchers (who both did not know the previous patient's evaluation) after having interviewed the patient about its pain intensity, so to reduce subjective statistical confounders. Patient's evaluation was accepted if it was not far from ± 1 point from the independent measures, otherwise replicated. Final evaluation was held by one of us (UT). The scale consisted of a horizontal line, with an interval ranging from 0 to 10, corresponding respectively to "no pain" (0) and "worst pain imaginable or severe (10)". Evaluations were performed before any O₂-O₃-AHT treatment and at one month following the end of the O₂-O₃-AHT.

Statistical Analysis

Collected data were expressed as mean \pm standard deviation, for quantitative values. Sample size was evaluated by assessing data and forecasting evaluations with Cohen *d* test and a Glass' *delta*. Statistical inference, if any, was evaluated following non-parametric tests and by a Kruskal-Wallis' test with $p < 0.05$ for score values from the 10 points-PI-NRS evaluation. Data were elaborated with a SPSS v. 24 software (SPSS Corp., Armonk, NY, USA) and Stata software for graphs.

Sample size calculation evaluating at least 132 patients needed to have a confidence level of 95% (CI₉₅) that the real value was within the 5% of the estimated value, so 200 subjects were largely exceeding this size. Considering a proportion of only 50% of positive outcomes, there was a 95% confidence interval chance that the correctness of our estimation was within the 6.95%, whereas for a proportion of 76%, the error was $\pm 5.93\%$ at CI₉₅.

The effect size calculation on pre-therapy and post-therapy data resulted a Cohen's *d* test (or Hedge's *g*) = 2.155056 and a Glass' *delta* test = 6.527027, therefore the difference between pre-therapy and post-therapy was higher than 2 standard deviations.

Cohen's *d* is the appropriate effect size measure if two groups have similar standard deviations and are both of the same size. Glass' *delta*, which uses only the standard deviation of the control group, is an alternative measure if each group has a different standard deviation. Hedges' *g*, which provides a measure of effect size weighted ac-

ording to the relative size of each sample, is an alternative where there are different sample sizes.

The study population was homogeneously represented. The margin of errors for the CI₉₅ of the evaluated data considering that 82.5% were female patients was $\leq 5.27\%$. For a correct proportion of 50% (females-males) the number of patients to be enrolled, so to be within the calculated margin of errors, was 346. The effect size calculation gave a Cohen's *d* test = 0.082359 and a Glass' *delta* = 0.073887, indicating a very small effect of the age distribution on the research study (< 0.2), even with 200 patients. For each evaluation, $p < 0.05$ was considered significant.

Results

Patients were all Caucasian (71% females 37.53 years ± 7.77 SD, 29% males 57.48 years ± 5.57 SD), all affected by fibromyalgia with 81% widespread muscle pain (WMP), 10% WMP with fatigue, 9% hyperalgesia. A quite complete rehabilitation of the musculoskeletal function and of the overall arthralgia was observed in 76% of the patients at one month of follow-up. Therefore, the number of sessions was adjusted to reach a quite complete disappearance of pain in the treated patient.

Following O₂-O₃-AHT, the reduction of arthralgia and generalized musculo-skeletal pain in female subjects was higher (5 score points, $H = 197.0164$, $p < 0.00001$) than in males (4 score points, $H = 32.2537$, $p < 0.00001$), despite the age ranges were comparable (44.68 ± 11.91 SD and 43.8 ± 9.30 SD years, respectively, $p = 0.28914$). Figure 1A shows that the activity of O₂-O₃-AHT on females and males resulted in different medians on the 11-point pain intensity Numerical Rating Scale (PI-NRS), i.e., 3 and 7, respectively, suggesting that the reduction of pain intensity in female patients was about three-fold higher than in males ($H = 86.194$, $p < 0.0001$). The effect of O₂-O₃-AHT on females did not appear to be affected by a different age clustering (Figure 1B).

Female patients with a mean age of 37.5 ± 7.77 SD (≤ 50 years old) showed a 10-PI-NRS post-treatment median = 3, as well as females with a mean age of 57.48 ± 5.57 SD (> 50 years old). Moreover, the highest 10-PI-NRS delta, i.e., from -9 to -7 score points, were quite homogeneously represented both in the younger (51 to 106 = 48.11%) and in the older cohorts (31 to 58 = 53.44%), as older people did not respond in a better and significant way than younger ones ($H =$

0.6952, $p = 0.40441$).

This would mean that O₂-O₃-AHT may work successfully despite the patient's age, which can be excluded as a statistical confounder.

Actually, the mode of the delta score (Δ_{PI-NRS}) in the younger cohort was 8, whereas in the older was 7, suggesting that younger FM patients had the highest and best performance in relieving pain and discomfort following O₂-O₃-AHT. The value of Δ_{PI-NRS} in the age range ≤ 30 years, was 6, therefore we can assume that the activity of pain relief and arthralgia disappearance exerted by O₂-O₃-AHT is not closely related with age.

In general, the number of patients having a reduction in the PI-NRS score from 10 (the maximal observed) to 3 (including 10-1 and 10-2) following only two runs of O₂-O₃-AHT was 23.5%, whereas only 17.5% did not show any significant improvement ($\Delta_{PI-NRS} = 0$ or 1), so assessing that the efficacy of O₂-O₃-AHT, independently from ages, encompassed at least 41% in a moderate way and 64.5% of the treated patients, as a whole. A net percentage of about 58% did not report any pain-related discomfort following one year after the last O₂-O₃-AHT treatment.

Discussion

In this study, more than three fourths of patients, ameliorated their arthralgic (pain and/or fatigue) symptoms following ozone therapy. Female patients responded better than males. Moreover, the application of 45 $\mu\text{g/ml}$ ozone in the O₂-O₃ major autohemotherapy, according to the SIOOT proto-

cols, resulted in the complete relieving of fibromyalgia symptoms, using a PI-NRS score ranking, in 23.5% of patients (by 7 score units) and in 17.5% (by 9 score units). About one fifth or more than one sixth of patients completely erased their symptomatology for a long-time following ozone therapy.

Respect to previous papers⁷ published by our group, we addressed the limitation of patients' cohort biased by an effect size due to paucity in the number of subjects enrolled in the study. Therefore, we increased the number of patients included in the clinical research, to fit a correct statistic.

The effect of the oxygen-ozone autohemotherapy on the majority of FM patients undergoing this therapeutic approach, was surprisingly beneficial: more than three quarters of patients suffering from generalized chronic pain passed from the worst pain felt (= 10) to more moderate form of arthralgia, evaluating their symptoms to a 10-score modified 11-score PI-NRS¹⁴.

A strong reduction in the level of pain occurred sensitively from one to two weeks following O₂-O₃-AHT and was maintained for at least four weeks from the first O₂-O₃-AHT, suggesting that the activity of ozone may be quite immediate and lasting. Considering that both diagnosis and treatment of FM are still considered as a fundamental matter of debate^{16,17}, the action here confirmed by ozone on FM is encouraging evidence and assessed our previously published results⁷.

So far, we have no reliable and sound explanation about the action of ozone therapy on FM patients. Possible suggestive hypotheses may come from the evidence that FM is closely related to oxidative stress and mitochondrial dysfunction¹⁸⁻²⁰,

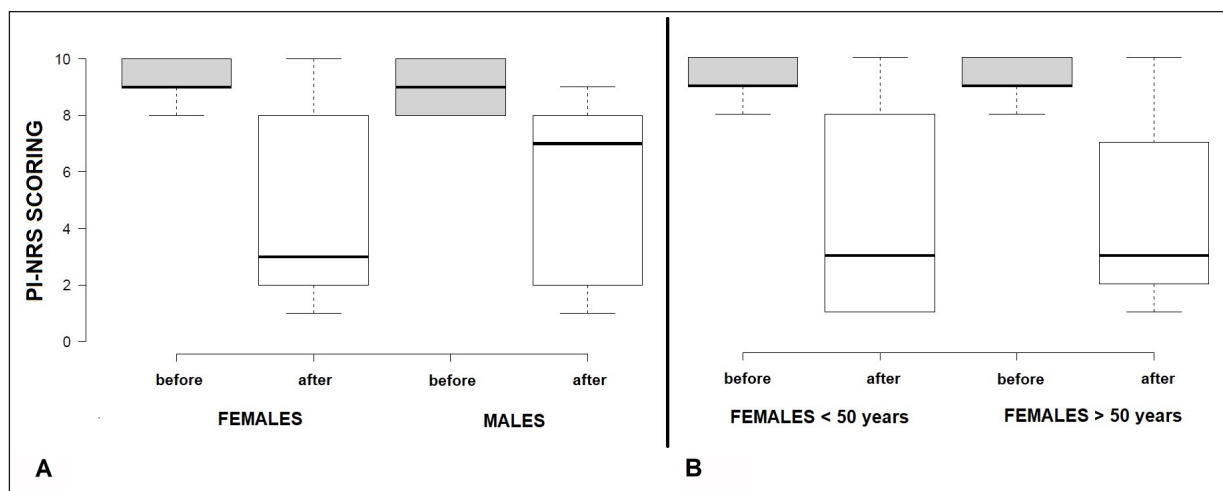


Figure 1. A, Effect of O₂-O₃-AHT on different sex distributions. B, Effect of O₂-O₃-AHT on different age classes.

for the modulation of which oxygen-ozone therapy represents a possible promising and successful tool²¹. The effect of ozone in several chronic disorders involving inflammation, fatigue and pain, has been recently explained as the possible participation of ozone-induced lipid mediators from blood, such as lipo-peroxides (LOPs), in activating mitohormesis and the Nrf2/Keap1/ARE signaling, which ultimately induce an antioxidant response, elicit mitochondria biogenesis and cell survival pathways and regulate the Th17/Treg immune balance²⁰⁻²⁴. A redox imbalance may be a major causative factor in many autoimmune-like and chronic pain syndromes²⁵.

In this perspective, it is suggestive the possible role exerted by ozone in the cerebrovascular physiology²⁶, as in FM a lower cerebral blood flow velocity was recently observed²⁷.

While the quite immediate effect of reducing the impact of the oxidative stress and its ability in triggering a pro-inflammatory phenotype is the “pain relief” signature of the O₂-O₃-AHT, its ability in triggering a correct immune balance CD4⁺ Th17/Treg by regulating the activity and biogenesis of mitochondria, may account for the long-lasting effects observed for the ozone therapy in FM^{7,24,28}. Very recently, some authors from the local University of Verona, suggested an autoimmune etiology for FM, previously indicated by others^{28,29}. If further confirmed, the O₂-O₃-AHT should work by modulating the complex balance Th17/Treg, as reported from other evidence coming from autoimmune diseases²⁹. Further insights are needed, to elucidate this fundamental issue.

The evidence here reported assesses the fundamental role of an integrative vision of the medical therapy, a vision that should be promoted both in physicians, experts, professionals and in patients, as well^{30,31}. Ozone is not a simple therapeutical drug but a modulation molecule able to interplay with the complex machinery of a cell.

Conclusions

Oxygen-ozone autohemotherapy (O₂-O₃-AHT) was proved to be a good therapeutic strategy to treat FM-caused pain, discomfort, fatigue and generalized arthralgia, so assessing previous results from ours with O₂-O₃-AHT on a limited number of patients. The evidence here reported is encouraging and shows how O₂-O₃-AHT is a promising approach to treat FM.

Conflict of Interest

The authors declare that they have no conflict of interest.

Informed Consent

All patients read, approved and signed an informed consent about the use of data for research purposes.

Ethics Approval

The study was conducted with the ethical approval of the Italian Society of Oxygen-Ozone Therapy (SIOOT), in compliance with the Helsinki Declaration.

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