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The effectiveness of major ozone autohemotherapy in the treatment of fibromyalgia syndrome

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This study was approved by the Kocaeli Derince Education and Research Hospital Ethics Committee (Project no: 2020-161)
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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Fibromyalgia syndrome (FMS) is a disease that seriously affects the quality of life. Although many modalities are used in treatment, there is still no common protocol. The aim of this study was to evaluate the effectiveness of major autohemotherapy (MAH) with ozone, which has come into use in recent years.

Methods: The retrospective cohort study included 45 male and female patients who were admitted to the Physical Medicine and Rehabilitation (PMR) outpatient clinic of Private Medar Hospital between January 2017 and October 2020 and were treated with MAH for a diagnosis of FMS. Evaluations were made before and after the last session of treatment using a visual analog scale (VAS), the Fibromyalgia Impact Questionnaire (FIQ) and the Short Form Health Survey-36 (SF-36). The scores of the patients were compared.

Results: Posttreatment VAS and FIQ scores decreased significantly (P = 0.014, P = 0.022 respectively) compared to pretreatment. After treatment, SF-36; PF, PH, EP, Fatigue, EW, SF, Pain, GH, HC scores increased significantly ($P < 0.05$ for all) compared to before treatment. The use of analgesics after treatment decreased significantly (P = 0.033) compared to before treatment.

Conclusion: MAH applied twice a week is an effective and practical method in the treatment of FMS.

Keywords: Fibromyalgia, Ozone, Hemotherapy, Oxidative stress, Pain

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Introduction

Fibromyalgia Syndrome (FMS) is a rheumatological disease characterized by widespread pain, fatigue, sleep disturbance, abnormal pain processing, and often psychological distress [1]. FMS generally affects women between the ages of 20-55 years and its prevalence in the whole population is 1.78% with a predominant ratio of women to men [2]. It has a very high personal and social impact and seriously impairs the quality of life of the patient [3].

Since the etiopathogenesis has not yet been clarified and the problems differ from patient to patient, there is currently no single, effective treatment method that provides full recovery of FMS. The treatments applied aim to reduce symptoms and maintain and improve quality of life and functions [4]. Methods using a single treatment modality cannot provide full effectiveness in FMS patients, and it is thought that the most effective method in clinical practice is multidisciplinary treatment [5]. Therefore, considering the patient's symptoms, applying both pharmacological and non-pharmacological approaches together would be an appropriate treatment approach [6].

Major ozone autohemotherapy (MAH), which is a simple and applicable method in the treatment of inflammatory and degenerative diseases related to the musculoskeletal system, has attracted attention in recent years. It differs from other treatment methods, because it is inexpensive, has almost no side-effects if applied correctly, offers a systemic treatment option, and is successfully applied in clinics. In MAH, the anti-inflammatory, anti-oxidative capacity activation and immunomodulation effects of ozone are utilized. Studies on the use of ozone therapy in musculoskeletal diseases started in the late 1980s with Verga [7] and Riva Sanseverino [8], and the number of studies have gradually increased. The highest level of evidence for the effects of ozone is in discogenic radiculopathies and osteoarthritis, especially in the knee [9].

From a scan of the literature, it can be seen that there have been limited studies in which ozone injections are applied in the treatment of FMS patients. Although positive effects have been observed in these studies, it has been emphasized that studies with greater patient numbers are needed.

The aim of this study was to determine the effectiveness of MAH in FM treatment with evaluations based on pain, quality of life, and FIQ scores.

Materials and methods

The study included 45 male and female patients who presented at the Private Gölcük Medar Hospital Physical Therapy and Rehabilitation outpatient clinic between January 1, 2017 and October 15, 2020, and underwent MAH for the diagnosis of FMS.

The study inclusion criteria were defined as patients diagnosed with FMS (examined by a PMR specialist and diagnosed with FMS according to the American College of Rheumatology (ACR) 1990 and 2010 classification criteria), aged 18-60 years, and provided a signed voluntary consent form to participate in the study [1, 10].

Patients with inflammatory rheumatic disease, primary psychiatric disease, pregnancy or a history of substance abuse, and patients who did not complete the ten-session treatment program were excluded from the study.

This study was approved by the Kocaeli Derince Education and Research Hospital Ethics Committee (Project no: 2020-161) and was carried out in compliance with the institutional guidelines and principles of the Declaration of Helsinki.

At the beginning of the study, a record was made for each patient including age, height, body weight, education level, smoking and alcohol habits, systemic diseases, duration of complaints, and medical treatment used for FMS. During the study, patients continued on their usual medication. All participants were assessed with a visual analog scale (VAS), the Fibromyalgia Impact Questionnaire (FEA) and SF-36 scales before and after treatment. It was recorded whether they used analgesics (paracetamol, NSAID) in the presence of pain. Exercise practices were also noted for patients who exercised regularly at least two days a week.

Evaluation of pain: The general pain status of the patients was evaluated with VAS [11]. Patients rated the intensity of pain on a scale from "0" (no pain) to "10" (worst possible pain).

Functional Evaluation: The Turkish version of the FIQ was used to evaluate the quality of life and functional status of the patients [12]. FIQ is a disease-specific tool for assessing the impact of fibromyalgia, and there is high evidence of its use in controlling the course of the disease [13, 14]. In this scale, ten different characteristics are measured, including physical functioning, the number of days patients felt well, the number of days patients were unable to work, work difficulty, pain, fatigue, morning tiredness, stiffness, anxiety and depression. With the exception of well-being, low scores indicate recovery or less affliction. The FIQ was completed by the patient and has a maximum score of 100.

Short Form Health Survey-36: The level of health-related quality of life was determined using the Short Form-36 (SF-36). This is the most widely used general quality of life scale and has proven Turkish validity and reliability [15]. It measures nine scales: physical functioning (PF), role physical (RP), pain (P), general health (GH), vitality (VT), social functioning (SF), role emotional (RE) mental health (MH) and health change (HC). High scores in all the subscales of the SF-36 reflect a better quality of life, and lower scores indicate deterioration in quality of life.

Application of major ozone autohemotherapy: In one session for each patient, the following were used: one bottle of vacuum sterile citrate, one blood collection set, one serum set, one intravenous cannula, and one ozone filter and one injector (50 cc) to remove ozone from the device. A blood sample of 100 mL was taken from the patient and prepared outside the body by enrichment with ozone at the right dose (10-50 GAMA) with special systems. The blood was then administered back to the patient at the recommended rate of 60-90 drops per minute. A total of ten sessions of MAH were applied as two sessions per week for five weeks [16].

Statistical analysis

Data obtained in the study were analyzed statistically using SPSS v 27.0 software. In the descriptive statistics of the data, mean, standard deviation, median minimum, maximum, frequency, and ratio values were used. The conformity of variables to normal distribution was assessed with the

Kolmogorov-Smirnov test. The Mann-Whitney U test was used in the analysis of quantitative independent data, and the Wilcoxon test was used for dependent quantitative data. Spearman correlation analysis was used. A value of $P < 0.05$ was considered statistically significant.

Results

The demographic data of the patients and the median values of the outcome measures are shown in Table 1.

Table 1: Demographic features and median values of outcome scores of FMS patients

		Values	
Age (years) mean (SD)		51.2	10.6
Gender	Female	41	91.1%
n %	Male	4	8.9%
Height (cm) mean (SD)		163.3	9.1
Weight (kg) mean (SD)		71.5	12.8
BMI (kg/m^2) mean (SD)		26.9	4.3
		n	%
Level of education	Primary school	19	42.2%
	High school	14	31.1%
	University	12	26.7%
Marital status	Single	2	4.4%
	Widowed	9	20.0%
	Married	34	75.6%
Smoking habit	(-)	34	75.6%
	(+)	11	24.4%
Alcohol consumption	(-)	38	84.4%
	(+)	7	15.6%
Exercise Habit	(-)	37	82.2%
	(+)	8	17.8%
Drug use for FMS	(-)	18	40.0%
	(+)	27	60.0%
Systemic disease	(-)	21	46.7%
	(+)	24	53.3%
Analgesic usage	No	17	37.8%
	Once a week	5	11.1%
	Everyday	23	51.1%
		Mean	SD
Ozone dose		32.9	3.8
VAS		6.3	1.4
FIQ		57.9	13.7
PF		67.6	15.8
RP		53.3	25.9
RE		54.1	28.7
VT		43.9	13.1
MH		57.1	13.6
SF		51.4	23.7
BP		35.7	15.9
GH		57.4	16.3
HC		41.7	16.0

SD: standard deviation, BMI: body mass index, VAS: visual analog score, FIQ: Fibromyalgia Impact Questionnaire, PF: physical functioning, RP: role limitations due to physical health, RE: role limitations due to emotional problems, VT: vitality, MH: mental health, SF: social functioning, BP: body pain, GH: general health, HC: health change

The posttreatment VAS score decreased significantly ($P = 0.014$) compared to pretreatment. The posttreatment FIQ score decreased significantly ($P = 0.022$) compared to pretreatment. After treatment, the SF-36 PF, RP, P, GH, VT, SF, RE, MH and HC scores increased significantly ($P < 0.05$ for all) compared to pretreatment. The level of analgesic use after the treatment decreased significantly ($P = 0.033$) compared to the pretreatment level. (Table 2)

The rate of change in VAS, FIQ, RP, P, GH, VT, SF, RE, MH and HC scores did not differ significantly between males and females after treatment ($P > 0.05$ for all). The posttreatment PF score increase in males was significantly ($P < 0.05$) higher than in females (Table 3).

The rate of change in VAS, FIQ, PF, RP, P, GH, SF, RE, MH, and HC scores after treatment did not differ significantly ($P > 0.05$ for all) between those who exercised and those who did not. The VT score increase in the exercising group was significantly ($P = 0.038$) lower than in the non-exercising group (Table 4).

Table 2: Comparison of analgesic use and outcome scores of patients before and after treatment

		Min	Max	Median	Mean	SD	*P*-value	
VAS								
Before Treatment		4.0	10.0	6.0	6.3	1.4	0.014	w
After Treatment		0.0	7.0	2.0	2.4	1.7		
FIQ								
Before Treatment		24.2	82.6	59.7	57.9	13.7	0.022	w
After Treatment		5.6	58.2	22.3	24.3	12.8		
PF								
Before Treatment		40.0	95.0	65.0	67.6	15.8	0.028	w
After Treatment		45.0	100.0	80.0	77.8	13.1		
RP								
Before Treatment		0.0	100.0	50.0	53.3	25.9	0.018	w
After Treatment		0.0	100.0	75.0	67.2	26.0		
RE								
Before Treatment		0.0	100.0	66.7	54.1	28.7	0.030	w
After Treatment		0.0	100.0	66.7	64.5	27.9		
VT								
Before Treatment		20.0	70.0	45.0	43.9	13.1	0.002	w
After Treatment		25.0	75.0	45.0	49.6	13.8		
MH								
Before Treatment		24.0	84.0	64.0	57.1	13.6	0.002	w
After Treatment		24.0	84.0	64.0	63.7	12.9		
SF								
Before Treatment		12.5	100.0	50.0	51.4	23.7	0.011	w
After Treatment		25.0	100.0	62.5	57.5	17.4		
BP								
Before Treatment		10.0	67.5	35.0	35.7	15.9	0.016	w
After Treatment		12.5	100.0	67.5	71.4	18.3		
GH								
Before Treatment		25.0	90.0	55.0	57.4	16.3	0.034	w
After Treatment		40.0	90.0	60.0	63.4	13.6		
HC								
Before Treatment		25.0	75.0	50.0	41.7	16.0	0.024	w
After Treatment		25.0	75.0	50.0	57.7	15.7		
Analgesic usage					n	%	*P*-value	
Before Treatment	*No*				17	37.8%	0.033	N
	Once a week				5	11.1%		
	Everyday				23	51.1%		
After Treatment	*No*				28	62.2%		
	Once a week				8	17.8%		
	Everyday				9	20.0%		

VAS: visual analog score, FIQ: Fibromyalgia Impact Questionnaire, PF: physical functioning, RP: role limitations due to physical health, RE: role limitations due to emotional problems, VT: vitality, MH: mental health, SF: social functioning, BP: body pain, GH: general health, HC: health change, W: Wilcoxon test, n: McNemar test

Table 3: Comparison of pre- and posttreatment outcome scores between males and females

Pre-Post Treatment Change %	Female Mean	Female SD	Female Median	Male Mean	Male SD	Male Median	*P*-value	
VAS	-64.0%	26.0%	-66.7%	-57.3%	26.0%	-64.6%	0.660	m
FIQ	-59.9%	17.6%	-65.1%	-49.1%	20.6%	-57.0%	0.232	m
PF	15.7%	21.9%	11.8%	54.6%	50.0%	40.3%	*0.034*	m
RP	30.9%	51.3%	0.0%	37.5%	47.9%	25.0%	0.628	m
RE	36.7%	77.0%	0.0%	-8.3%	16.7%	0.0%	0.206	m
VT	16.7%	40.0%	0.0%	45.0%	90.0%	0.0%	0.892	m
MH	18.0%	45.2%	0.0%	18.1%	30.5%	8.3%	0.947	m
SF	30.3%	64.0%	0.0%	46.4%	74.3%	25.0%	0.724	m
BP	159.9%	214.5%	89.5%	200.0%	122.5%	200.0%	0.144	m
GH	14.8%	28.9%	7.7%	23.2%	20.5%	18.1%	0.266	m
HC	51.0%	63.7%	40.0%	87.5%	85.4%	75.0%	0.308	m

VAS: visual analog score, FIQ: Fibromyalgia Impact Questionnaire, PF: physical functioning, RP: role limitations due to physical health, RE: role limitations due to emotional problems, VT: vitality, MH: mental health, SF: social functioning, BP: body pain, GH: general health, HC: health change, m: Mann-Whitney U test

Table 4: Comparison of pre- and posttreatment outcome scores between groups that exercised regularly and those who did not

Pre-Post Treatment Change %	Exercises (-) Mean	Exercises (-) SD	Exercises (-) Median	Exercises (+) Mean	Exercises (+) SD	Exercises (+) Median	*P*-value	
VAS	-63.0%	23.8%	-66.7%	-65.2%	35.3%	-75.0%	0.512	m
FIQ	-59.1%	17.8%	-61.7%	-58.3%	19.5%	-62.1%	1.000	m
PF	19.4%	25.6%	14.3%	18.1%	35.0%	2.8%	0.259	m
RP	30.2%	45.1%	0.0%	37.5%	74.4%	0.0%	0.634	m
RE	31.5%	75.7%	0.0%	37.5%	74.5%	0.0%	0.596	m
VT	23.6%	49.2%	0.0%	-1.3%	3.5%	0.0%	0.038	m
MH	21.9%	47.6%	0.0%	0.0%	0.0%	0.0%	0.086	m
SF	39.2%	68.6%	20.0%	-2.5%	7.1%	0.0%	0.051	m
BP	182.6%	223.1%	100.0%	74.9%	58.6%	49.1%	0.118	m
GH	18.0%	30.5%	7.7%	4.2%	5.9%	0.0%	0.114	m
HC	60.5%	67.9%	50.0%	25.0%	46.3%	0.0%	0.137	m

VAS: visual analog score, FIQ: Fibromyalgia Impact Questionnaire, PF: physical functioning, RP: role limitations due to physical health, RE: role limitations due to emotional problems, VT: vitality, MH: mental health, SF: social functioning, BP: body pain, GH: general health, HC: health change, m: Mann-Whitney U test

The rate of change in VAS, FIQ, PF, RP, P, GH, VT, SF, RE, MH, and HC scores did not differ significantly ($P > 0.05$ for all) after treatment between those using and not using drugs for FMS (pregabalin, gabapentin, duloxetine, selective serotonin reuptake inhibitor (SSRI), tricyclic antidepressant) (Table 5).

Table 5: Comparison of pre- and posttreatment outcome scores between groups that used and did not use drugs for FMS

Pre-Post Treatment Change %	Drug use for FM (-) Mean	SD	Median	Drug use for FM (+) Mean	SD	Median	*P*-value	
VAS	-68.2%	25.8%	-71.4%	-60.2%	25.7%	-62.5%	0.285	m
FIQ	-60.7%	19.0%	-65.5%	-57.8%	17.4%	-59.4%	0.517	m
PF	15.3%	17.7%	14.8%	21.7%	31.9%	11.8%	0.814	m
RP	25.9%	34.4%	0.0%	35.2%	59.3%	0.0%	1.000	m
RE	49.1%	88.0%	0.0%	21.2%	63.1%	0.0%	0.347	m
VT	23.1%	49.8%	0.0%	16.6%	43.2%	0.0%	0.472	m
MH	26.5%	43.9%	3.1%	12.4%	43.7%	0.0%	0.051	m
SF	44.4%	80.0%	0.0%	23.4%	50.9%	0.0%	0.933	m
BP	96.2%	84.6%	61.1%	208.3%	250.7%	107.7%	0.131	m
GH	20.7%	35.0%	8.4%	12.1%	22.6%	7.7%	0.565	m
HC	63.3%	63.9%	50.0%	48.1%	67.2%	0.0%	0.283	m

VAS: visual analog score, FIQ: Fibromyalgia Impact Questionnaire, PF: physical functioning, RP: role limitations due to physical health, RE: role limitations due to emotional problems, VT: vitality, MH: mental health, SF: social functioning, BP: body pain, GH: general health, HC: health change, m: Mann-Whitney U test

Discussion

The aim of this study was to reveal the efficacy of MAH in the treatment of FMS by evaluating its effect on quality of life, functional status, and pain of the patients.

FMS is known to be much more common in females, and of the 45 patients included in this study, 41 (91.1%) were female and 4 (8.9%) were male [2].

In a study published in 2019, in which MAH was applied to 20 FMS patients, there was reported to be a significant decrease in the number of trigger points, FIQ scores, and oxidative stress markers in the blood, as well as an increase in sleep quality and mental awareness [17]. In the current study, there was also a statistically significant decrease in the FIQ score after treatment compared to the pretreatment scores.

In another study published in 2019, which included 65 FMS patients, MAH was applied to 55 patients and rectal ozone was applied to 10 patients. The results were evaluated with the numeric rating scale (NRS) and Fatigue Severity Scale (FSS). Posttreatment, a significant decrease in NRS, and scores was observed in 45 (70%) of the patients [18]. In the current study, the posttreatment VAS scores decreased significantly compared to pretreatment. This result was also reflected in the significant decrease in the use of analgesics in the posttreatment period.

No previous studies have investigated the efficacy of ozone therapy in FMS that has evaluated quality of life with SF-36. Tirelli et al. applied MAH to 30 patients and rectal ozone to 10 patients with FMS, and reported a decrease of more than 50% in the NRS and FSS scores in 80% of patients [19].

In a case report published in 2017, MAH was applied twice a week to a 45-year-old female patient with FMS. In the components of the Fibromyalgia Survey Questionnaire, the Widespread Pain Index decreased from 15 to 7, and the Symptoms Severity Scale from 7 to 1 at the end of 12 sessions [20].

The etiopathogenesis of FMS is still unclear, so a number of causes and mechanisms are still cited, one of which is that oxidative stress may play a role [21]. Therefore, MAH has gained a place in the treatment of FMS due to its antioxidant effect. Ozone rapidly transforms into molecular oxygen and oxygen radicals in biological environments, creating a moderate level of oxidative stress in the body. In this way, ozone is perceived as an oxidative threat in the body, which results in the stimulation of enzymes working in antioxidant defense systems. Moderate oxidative stress activates nuclear factor erythroid 2-related factor-2 (Nrf-2) and this triggers the transcription of antioxidant response elements (ARE). However, severe oxidative stress causes an inflammatory response by activating nuclear factor kappa B and ultimately tissue destruction by increasing cyclooxygenase 2, prostaglandin E2 and cytokine production [12].

The key point in ozone therapy is the regulation of the oxidative stress level [22]. As a result, ozone therapy has an antioxidant effect at the appropriate dose. The ozone dose should be sufficient to produce an acute, clear, and temporary oxidative stress. Lower doses cause a placebo effect, and higher doses cause toxicity [23]. Therefore, it is very important to set ozone doses correctly. Despite attempts to determine the optimal dose and safe range from the results of animal studies on ozone-oxygen concentrations, application volumes and the number of applications, a common consensus could not be achieved. However, the general opinion is that applications are started at low concentrations and the concentration is increased if necessary [24].

In the current study patients the treatment was started at a low dose (15-20 gamma) and gradually increased. The treatment was then continued at the dose at which the patient's complaints were minimized (40-50 gamma). The mean ozone dose was 33.5 (32.8 [3.8]) gamma and no side-effects were observed in any of the patients included in this study.

Three new clinical trials involving fibromyalgia patients were included in the 2017 Cochrane review, evaluating the role of physical activity and exercise in the treatment of chronic pain.

Despite the low level of evidence in the review, it was concluded that physical activity and exercise were beneficial at a mild to moderate level in terms of reducing the severity of pain and improving physical functions in general, as well as improving the quality of life with few undesirable effects [25]. In the current study, the increase in vitality score was significantly lower in the exercising group than in the non-exercising group.

Conclusion

MAH has been widely used in recent years, especially in chronic pain syndromes. We also observed positive and significant results in the treatment of FMS in our study. The most important limitation of this study was the absence of a control group and long-term follow-up results. No randomized controlled study could be found in the literature that has investigated the efficacy of ozone therapy in FMS patients. In addition, there is no common approach regarding the ozone dose to be applied in FMS. There is, therefore, a need for further randomized controlled studies with longer follow-ups and the creation of a general approach to dosage to be able to further illuminate the place of ozone therapy in FMS.

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