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Effect of Ozone Therapy on Pain, Depression and Quality of Life in Patients with Fibromyalgia Syndrome

Fibromiyalji Sendromlu Hastalarda Ozon Tedavisinin Ağrı, Depresyon ve Yaşam Kalitesi Üzerine Etkisi

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ÖZET

Amaç: Bu çalışmada, fibromiyalji sendromlu (FMS) hastalarda ozon tedavisinin ağrı, depresyon ve yaşam kalitesi üzerine etkisini araştırmayı amaçladık.
Gereçler ve Yöntem: Çalışmaya FMS tanısı konulan ve fizyoterapiye ek ozon tedavisi uygulanan 18-65 yaş arası toplam 70 kadın hasta dahil edildi. Yaş, cinsiyet gibi demografik veriler ve Vizüel Analog Skala(VAS), Beck Depresyon İndeksi(BDE) ve Fibromiyalji Etki Anketi(FIQ) gibi klinik parametreler retrospektif olarak analiz edildi. Hastalar ozon ve kontrol grubu olarak iki gruba ayrıldı. Kontrol grubundaki hastalara 3 hafta klasik fizik tedavi (hotpack, TENS) uygulandı. Ozon terapi grubunda ise klasik fizik tedavi ile eş zamanlı olarak üç hafta süreyle majör otohemoterapi yöntemi uygulandı. Her iki grup tedavi öncesi ve sonrası ağrı şiddeti için VAS, depresyon için BDE ve yaşam kalitesi için FIQ açısından karşılaştırıldı.
Bulgular: Ozon ve kontrol grubu arasında sırasıyla, yaş (36,68±2,84/35,85±3,77) (p:0,626) ile vücut kitle indeksi (VKİ) (23,78±2,41/23,65±2,70) (p:0,728) arasında anlamlı fark yoktu. Her iki grupta tedavi öncesine göre, tedavi sonrası ağrı şiddeti (p<0,001), depresyon (p<0,001) ve yaşam kalitesi (p<0,001) düzeylerinde anlamlı olarak iyileşme gözlenirken, tedavi sonrası bu parametrelerde ozon grubunda daha iyi düzelme gözlendi (p< 0,001).
Sonuç: Çalışmamız, ozon tedavisinin FMS'li hastalarda ağrı şiddeti, depresyon ve yaşam kalitesi üzerine daha iyi etkilerinin olduğunu göstermiştir. Bu nedenle tedaviye güvenle eklenebilir.

Anahtar Kelimeler: Fibromiyalji, ozon tedavisi, ağrı, fizik tedavi, yaşam kalitesi

ABSTRACT

Aim: In this study, we aimed to investigate the effect of ozone therapy on pain, depression and quality of life in patients with fibromyalgia syndrome (FMS).
Materials and Method: A total of 70 female patients aged 18-65 who were diagnosed with FMS and received ozone therapy in addition to physiotherapy were included in the study. Demographic data such as age, gender, and clinical parameters such as Visual Analague Scalae(VAS), Beck Depression Index(BDI) and Fibromyalgia Impact Questionnaire(FIQ) were analyzed retrospectively. Patients were divided into two groups as the ozone and control groups. Patients in the control group were administered classical physical therapy (hotpack, TENS) for three weeks. Whereas, the major autohemotherapy method was applied in the ozone therapy group simultaneously with the classical physical therapy again for three weeks. Both groups were compared in terms of VAS for pain severity, BDI for depression, and FIQ for quality of life in before and after the treatment.
Results: There was no significant difference between age (36,68±2,84/35,85±3,77) (p:0,626) and body mass index (BMI) (23,78±2,41/23,65±2,70) (p:0,728) between the ozone and the control group respectively. Pain severity (p<0,001), depression (p<0,001) and quality of life (p<0,001) were significantly improved after treatment in both groups compared the before treatment, while better improvement was observed in the ozone group after treatment (p<0,001).
Conclusion: Our study demonstrated that ozone therapy has better effects on pain severity, depression and quality of life in patients with FMS. Therefore it can be added to treatment safely.

Key words: Fibromyalgia, Ozone therapy, Pain, Physical therapy, Quality of life

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INTRODUCTION

Fibromyalgia syndrome (FMS) is a chronic rheumatologic disease with unknown cause characterized by widespread pain, fatigue, depression, sleep disturbance and anxiety. The pathogenesis of FMS is not fully understood, although both genetic and environmental factors play a role in the pathogenesis of the disease (1). Although debate on the definition of FMS and whether it is a real disease is ongoing, symptoms of the patients are real and pain and mood disorders that occur in patients with FMS affect the functional status and impair the quality of life (2).

Ozone (O_3) is a natural, colorless but unstable molecule consisting of three oxygen atoms, that is gaseous at room temperature, has a specific odor and is a chemical derivative of oxygen. Whereas, ozone gas used in treatment is obtained by a strong electrical force applied on oxygen atoms in ozone generators. Ozone gas reacts with biomolecules in the environment where it is applied, leading to the formation of reactive oxygen species (ROS) and lipid peroxidation products. Owing to these products with a high oxidative stress capacity, ozone therapy controls oxidative stress status of the body, increasing antioxidative capacity and modulating the immune system (3). Among the mechanisms of action that are most commonly emphasized for ozone therapy are its antimicrobial action and systemic hemostasis repairing effect. Bactericidal, virucidal and fungicidal are shown as its antimicrobial effects. On the other hand, ozone therapy has several systemic effects including the regulation of microcirculation, restoration of capillary permeability and oxygen carrying function of the blood, decreasing blood coagulation, stimulating antioxidant system, analgesic, antiinflammatory and immunomodulatory effects (4).

Ozone therapy is one of the complementary medicine methods used in different branches in the treatment of many chronic diseases in recent years and its use is increasingly becoming widespread. Ozone hemotherapy is used in inflammatory and degenerative diseases associated with the musculoskeletal system due to its analgesic-antiinflammatory effects, activation of antioxidative capacity and immunomodulation effects (5). Clinical studies evaluating the effects of ozone on the musculoskeletal system are gradually increasing (6,7,8). However, the number of studies in the literature evaluating ozone therapy in fibromyalgia is limited. Therefore, the objective of our study was to investigate the effects of ozone therapy on pain, depression and quality of life in female patients with FMS.

MATERIAL AND METHODS

Study Design and Patients

This study was a retrospective analysis of patients who presented to the physical therapy and rehabilitation outpatient clinic and were diagnosed with FMS according to the 2016 criteria of the American College of Rheumatology and received ozone therapy in addition to physiotherapy between July 2018 and December 2019. Files of the patients were retrospectively screened. According to the collected data, a total of 70 patients who met the inclusion criteria were included in the study. Then the patients were divided into two groups (35 in each group). Patients who received classical physical therapy (CPT) with hotpacks and TENS were assigned to the control group and those who received ozone therapy in addition to CPT to the ozone group. This study was conductedin accordance with the principles of the Declaration of Helsinki and the ethics approval was received from local ethics committee.

Only female patients with a Visual Analogue Scale (VAS) score >5, aged 18-65, diagnosed with fibromyalgia for the last 2 years, were included in our study. Patients with a chronic diffuse pain related disease other than FMS, those who previously received ozone therapy, physiotherapy, patients with bleeding diathesis or those receiving anticoagulant therapy, patients with hyperthyroidism, those receiving psychological therapy, pregnant women or who were in the lactation period, and those with accompanying comorbidity and malignancy were excluded from the study.

Application

Patients in the control group were administered CPT (20 minutes hotpacks and 30 minutes transcutaneous electrical nerve stimulation (TENS) at convensional mode with 200Hz, 10-30A 100 pulses included in 1 session) for three weeks. Whereas, the major autohemotherapy method was applied in the ozone therapy group simultaneously with the CPT again for three weeks. Ozone application, which has an increasing frequency of application in recent years, can be performed in two forms as systemic and topical. Systemic forms include major autohemotherapy, minor autohemotherapy, rectal ozone application and intravenous applications. Among these, the most commonly applied are major and minor auto-therapies. In major autohemotherapy, 50 to 100 ml of blood drawn from the patient is mixed with an ozone-oxygen compound of an equal volume and at an appropriate dose with special systems under sterile conditions in the outer environment. This prepared mixture is then given to the patient again via the intravenous route (5). Major autohemotherapy was applied in this study. Although dose range used in the systemic treatments is usually between 20-80 µg/mL, in our study we used a dose of 20-50 µg/mL (9). The treatment was initiated with a dose of 100 cc venous blood and 20 µg/mL ozone-oxygen, and the therapeutic dose was increased by evaluating complaints of the patient at each session. Major therapy was applied two times a week and physical therapy daily. Patients' pain scores, depression levels

and daily life activities were questioned before and after the treatment. Ozone therapy of the patients was performed by the same physician who had a 5-year clinical experience in the field of ozone therapy.

Evaluations

Treatment measurements were repeated two times as before and after the treatment in both groups by the same physician in order to evaluate effectiveness of the treatment. Severity of pain and fatigue was evaluated using the Visual Analogue Scale (VAS). The scale consists of a 10-cm ruler with '0' corresponding to no pain and fatigue on one end, and '10' corresponding to the most severe pain and fatigue on the other end. Patients mark on the ruler according to their pain status. Numerical value indicates pain level of the patient. Increased score indicates a high level of pain and fatigue (10). The presence and level of depression in patients were evaluated with the Beck Depression Index (BDI). BDI is a depression grading scale consisting of a total 21 questions evaluated by summing the points between 0 and 3 that are obtained from each answer. The scores ≥10 points are evaluated in favour of depression (11).

QoL of the patients was evaluated with the Fibromyalgia Impact Questionnaire (FIQ). FIQ is evaluated with 10 separate features including physical function, feel good, missed work, do work, pain, fatigue, rested, stiffness, anxiety and depression. Maximum score for each subscale is 10 and the total maximum score is 100. A high score indicates negative effects caused by the disease (12).

Statistical analysis

Data in the study were expressed as mean ± standard deviation (mean±SD) and categorical data with percentage (%). Normality of the data was evaluated with Kolmogorov-Simirnov test, intra-group paired comparisons with the Paired Sample t test and intergroup comparisons with independent Student-t test. The statistical analysis was performed using SPSS v. 22.0 (IBM, Chicago, Illinois USA) package software. $p<0.05$ values were considered statistically significant.

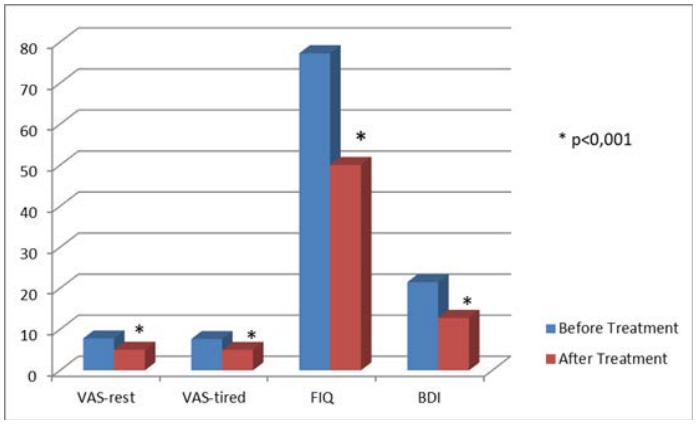

Figure 1. Clinical changes in the control group before and after treatment

RESULTS

The mean age was found 36,68±2,84 years in the ozone therapy group and 35,85±3,77 years in the control group. In addition to the sociodemographic questioning form, VAS, FIQ and BDI forms were filled by the patients in both groups. When educational status of the patients was evaluated; 39.1% were primary school graduates, 18.8% middle school graduates, 17.4% high school graduates and 24.6% college graduates. Of all patients, 29% were working and the remaining participants were housewives. No significant difference was found between the ozone therapy and control groups in terms of age (p:0.626) and body mass index (BMI) (p:0.728). In the evaluation of before and after treatment; VAS-pain, VAS-fatigue, FIQ and BDI scores were significantly decreased in both groups ($p<0.001$). Demographic and clinical features of the patient and control groups are shown in Table 1, and clinical changes between before and after treatment in Figures 1 and 2. No significant side effect was observed in any patient during the treatment.

In the intergroup comparison; there were statistically

Table 1. Demographic and clinical features of the ozone and control groups

n:70	Control group (n:35) (CPT)	Ozone group (n:35) (CPT+OT)	p
Age (years)	35,85±3,77	36,68±2,84	0,626
BMI (Kg/m²)	23,65±2,70	23,78±2,41	0,728
VAS (BT)	7,79±0,72	7,88±0,79	0,625
VAS (AT)	5,02±0,86	3,54±0,81	<0,001
VAS fatigue (BT)	7,61±0,85	7,82±0,95	0,322
VAS fatigue (AT)	4,97±0,97	3,76±0,91	<0,001
FIQ (BT)	77,26±2,87	75,77±1,98	0,457
FIQ (AT)	50,05±3,62	34,15±2,45	<0,001
BDI (BT)	21,50±3,72	22,13±2,05	0,577
BDI (AT)	12,79±2,07	9,82±1,38	<0,001

BMI: Body mass index, VAS: Visual analogue scale, BT: Before treatment, AT: After treatment, FIQ: Fibromyalgia impact questionnaire, BDI: Beck depression index

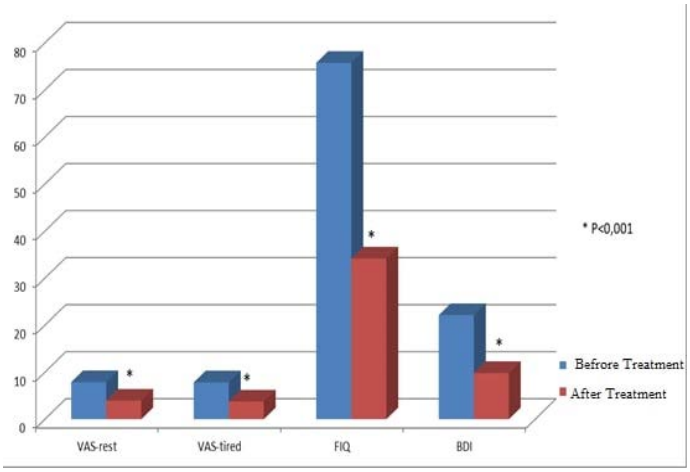

Figure 2. Clinical changes in the ozone group before and after treatment

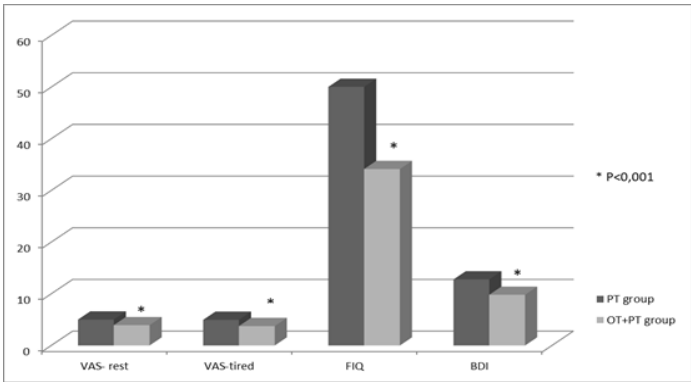

Figure 3. Changes of the scores between the group

significant differences in all scores in the ozone group compared to the control group (for all p<0.001). Comparison of the clinical scores of both groups after the treatment is shown in Figure 3.

DISCUSSION

FMS is a chronic musculoskeletal system disease with unknown etiopathogenesis, which affects daily life activities and functional status with accompanying symptoms such as widespread body pain, fatigue, morning stiffness, depression, sleep disturbances and anxiety (13). Because it is mostly seen in adult and productive age groups, FMS causes substantial work loss and treatment costs. Pain and mood disorders developed in FMS patients affect functional status, impairing quality of life (14).

Because o the existing treatment methods focus on symptoms and a complete recovery can not be achieved, treatment of FMS, which is a chronic pain disorder with a complex etiopathogenesis, is challenging. In recent years, alternative methods have been introduced in line with the new information in the mechanism of action. Medical treatment methods remain the major treatment options. In addition, ozone therapy is one of the traditional and complementary medical methods, which is frequently used in FMS, and is effective on pain, fatigue and depression (13).

Ozone therapy is a treatment method used in many diseases using different implementation techniques and with a low side effect incidence. Ozone molecule (O3) consists of three oxygen atoms and is the known most powerful oxidant agent (15). Both arterial and venous micro-circulations are improved with ozone therapy. Ozone causes an increase in the elasticity of erythrocytes, allowing more tissue transition in the capillary area and leading to an increase in tissue oxygenation. It increases antioxidative capacity through peroxides, shows analgesic and antiinflammatory effects and triggers cellular regeneration (16).

Although there is evidence that oxidative stress increases in fibromyalgia, the reason for this is not fully understood. Studies have been conducted with the assumption that ozone has mechanisms of action including oxidative stress suppressing, namely antioxidant effect and systemic hemostasis repairing effect, increasing oxygenation by regulating the circulation and modulating the immune system (5). Therefore, the objective of our study was to evaluate the effectiveness of ozone therapy in addition to the existing therapy in fibromyalgia.

The number of studies about the use of ozone applications in musculoskeletal system diseases has been increased in recent years. Antiinflammatory, anti-oxidative capacity activating and immunomodulation effects of ozone therapy are utilized in musculoskeletal system related diseases (5). The remarkable effect of the ozone effect has been shown in several studies, and this effect is due to the fact that ozone activates many metabolic pathways. In a study by Magalhaes et al. (17) in patients with lower back pain due to lumbar discopathy, ozone administration to the intradiscal and paravertebral muscles was found to reduce pain level. In another study by Özcan et al. in patients with chronic lower back pain, VAS and ODI (Oswestry Disability Index) values of the patients were significantly decreased after ozone therapy of 6 sessions (18). The reason for ozone being effective in lower back pain and disc pathologies is providing oxygenation within the disc by ozone gas entering into the nucleus pulposus, reducing the disk volume by decreasing the fluid in the disc and eliminating the pressure on the nerve root. In paravertebral injection method, ozone gas is rapidly dissolved in the interstitial area, reacting with antioxidants. It increases oxygenation in the muscle, improves local acidosis, and shows a spasm reducing effect by increasing venous and lymphatic circulation (19). In another study, intraarticular ozone injection was found to

be effective on pain, functional capacity and QoL in patients with osteoarthritis (20). The mechanism of action of ozone therapy in these studies was via increasing oxygenation and facilitating circulation, providing release of cytokines such as interleukin-10 and transforming growth factor-b through the formed peroxides, and thus, producing chondrocyte and matrix proliferation and leading to increasedsynthesis of articular cartilage (19, 21, 22).

Ozone application is applied in various ways as local and major but these are different things. We in our study, we evaluated the application of major ozone in patients with fibromyalgia. Looking at the literature, it is seen that the number of studies on the use of ozone injections in fibromyalgia patients is limited. In a study by Hidalgo-Tallon using ozone therapy in patients with fibromyalgia, significant improvements were achieved in depression and QoL of the patients after the treatment (23). In one of two studies performed by Tinelli et al. (24) in patients with fibromyalgia vast majority of symptoms were found to be decreased in 80% of the patients with major homeopathy and rectal ozone application, while in the second study complaints of the patients were largely disappeared in 70% of 65 patients with fibromyalgia and no side effect was observed with major and rectal ozone application (25). In a study by Moreno-Fernandez et al. (26) on 20 patients with fibromyalgia, major homeopathy was performed and pain, fatigue and FIQ levels of the patients were decreased as a result of the treatment. In the same study, serotonin level was increased, while the levels of ROS and LOPs were decreased. Serotonin level is low in patients with fibromyalgia. Serotonin is an inhibitory neurotransmitter playing a role in providing sleep and perceiving pain. Since the level of serotonin is low in FMS, it is accepted that the conditions such as pain, anxiety, and insomnia in patients are related to serotonin deficiency (27). In the mentioned study, increased serotonin level might have contributed to the decreased FIQ level. Similarly to the above mentioned studies, in our study pain, depression and fatigue and FIQ levels of the patients were decreased in FMS patients. We think that, in our study also clinical conditions were improved due to the mentioned mechanisms of action of ozone therapy. In addition, unlike the other studies our study was conducted only with female patients and compared physiotherapy and ozone therapy.

Limitations of our study may include the relatively small number of patients and lack of long-term follow-up. In addıtıon, our study does not include mid-long-term follow-up results can be considered as an important limitation.

In conclusion, our study, in which we evaluated effectiveness of ozone therapy in female patients with FMS, demonstrated that a combination of ozone and physical therapies were more effective in decreasing symptoms such as pain, fatigue and depression, and increasing quality of life. According to the studies performed ozone therapy should be considered an effective and safe treatment option in FMS patients in addition to other existing treatment methods or when adequate outcomes can not be obtained with the other options, and should be used as a complementary and effective treatment option.

Etik Kurul: Ethical approval was obtained for this study from the local ethics committee with the decision dated 24.04.2020 and numbered 2020/03-51.

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