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Original Article

Comparison of the efficacy of oxygen-ozone and lidocaine injections in the treatment of myofascial pain syndrome: A randomized clinical trial

Nurdan Korkmaz[1], Merve Örücü Atar[1], Sinem Uyar Köylü[1], Sefa Gümrük Aslan[1], Özge Tezen[2], Serdar Kesikburun[3]

[1]Department of Physical Medicine and Rehabilitation, Health Sciences University, Gaziler Physical Medicine and Rehabilitation Training and Research Hospital, Ankara, Türkiye
[2]Department of Physical Medicine and Rehabilitation, Ankara City Hospital, Ankara, Türkiye
[3]Department of Physical Medicine and Rehabilitation, Health Sciences University, Gülhane School of Medicine, Gaziler Physical Medicine and Rehabilitation Training and Research Hospital, Ankara, Türkiye

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ABSTRACT

Objectives: This study aims to compare effectiveness of oxygen-ozone injection versus lidocaine injection on the trigger point in the treatment of myofascial pain syndrome (MPS).

Patients and methods: Between April 2021 and December 2021, a total of 46 patients with MPS (8 males, 38 females; mean age: 44.7±10.4 years; range, 25 to 65 years) were included. The patients were randomized to either ozone injection (n=23) or lidocaine injection (n=23) groups. All injections were administered once a week for three consecutive weeks. The primary outcome measure was the pain severity assessed by Visual Analog Scale (VAS). Secondary outcome measures were cervical lateral flexion range of motion (ROM), pain score (PS), and Neck Disability Index (NDI). The measurements were performed before the treatment, and at four and 12 weeks after treatment.

Results: There was a significant effect of time for VAS, PS, and NDI scores in both groups. Compared to baseline versus Weeks 4 and 12, the VAS, PS, and NDI scores significantly decreased over time in both groups ($p<0.001$ for all). A significant group × time interaction was identified regarding the VAS scores. The mean difference in the VAS scores over time was significantly higher in the lidocaine group compared to the oxygen-ozone group ($p=0.028$).

Conclusion: Oxygen-ozone and lidocaine injections of the trigger point can effectively improve pain and functional status. However, lidocaine injection appears to be superior in reducing pain compared to oxygen-ozone injection, but is not superior in improving function and PS.

Keywords: Function, lidocaine injection, myofascial pain syndrome, oxygen-ozone injection.

Myofascial pain syndrome (MPS), known as a regional pain syndrome, constitutes an important part of chronic musculoskeletal pain.[1] It is seen in 45 to 54% of the general population.[2] It is characterized by the presence of trigger points and tender areas in the muscles or related connective tissue and, sometimes, with a local twitch response following palpation of the trigger point.[1] The prevalence of trigger points in patients admitted to clinics due to chronic widespread pain ranges from 30 to 93%.[3]

Myofascial pain syndrome has been attempted to be treated using a wide variety of non-invasive (oral analgesics, exercises, physical therapy modalities such as ultrasound, transcutaneous electrical stimulation, infrared, and massage) and invasive (corticosteroids, dry needling, local anesthetics and botulinum toxin injections) methods.[4] Travell and Simons suggested that inactivating the trigger point was an important component for successful treatment of the pain syndrome.[5] In the literature,

Corresponding author: Nurdan Korkmaz, MD. SBÜ Ankara Gaziler Fizik Tedavi ve Rehabilitasyon Eğitim ve Araştırma Hastanesi, Fiziksel Tıp ve Rehabilitasyon Kliniği, 06800 Bilkent, Ankara, Türkiye.

E-mail: nurizkorkmaz@hotmail.com

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injection methods were found to be more beneficial in terms of reaching the muscles and providing a longer analgesic effect.[6] Therefore, previous studies have focused on trigger point injection methods and compared efficacy of various injection methods in the treatment of MPS.[7-10] Although there are controversial results regarding their superiority over each other,[7,11] local anesthetic injection has long been known as one of the most widely applied and effective choice in the treatment of MPS.[8-10,12] Despite these broad therapeutic options, no consensus has been reached for the treatment of MPS and this remains a challenging area.[13]

Ozone, a gas molecule containing three oxygen atoms in a dynamically unstable structure, has antioxidative, immune-modulatory, bactericidal, analgesic, and anti-inflammatory biological effects.[14] Recent studies have proposed oxygen-ozone injection as a treatment option of some patients with musculoskeletal disorders such as knee osteoarthritis,[15] low back pain,[14] tendon pathologies,[16] and carpal tunnel syndrome.[17] However, a few studies are available using oxygen-ozone injection in the treatment of MPS.[18] To the best of our knowledge, only Raeissadat et al.[8] evaluated the role of oxygen-ozone injection in the treatment of MPS patients with an active trigger point in the upper trapezius muscle. They compared oxygen-ozone and lidocaine injections with dry needling and followed the efficacy of the treatments for four weeks. In the light of current data, in the present study, we aimed to examine the efficacy of oxygen-ozone injection applied to the trigger point in the trapezius muscle in the treatment of MPS and to compare effectiveness of oxygen-ozone versus lidocaine injection with 12-week follow-up.

PATIENTS AND METHODS

This single-center, single-blind, prospective, randomized clinical study was conducted at Gaziler Physical Medicine and Rehabilitation Training and Research Hospital, Department of Physical Medicine and Rehabilitation between April 2021 and December 2021. Patients who were admitted to our clinic with neck pain and diagnosed with MPS according to the criteria defined by Simons and Travell[5] were included in the study. Patients who volunteered to participate in the study were evaluated for eligibility. Inclusion criteria were as follows: age between 18 and 65 years; symptoms lasting for at least three months; active trigger points and/or at least one taut band on manual palpation in the upper trapezius;

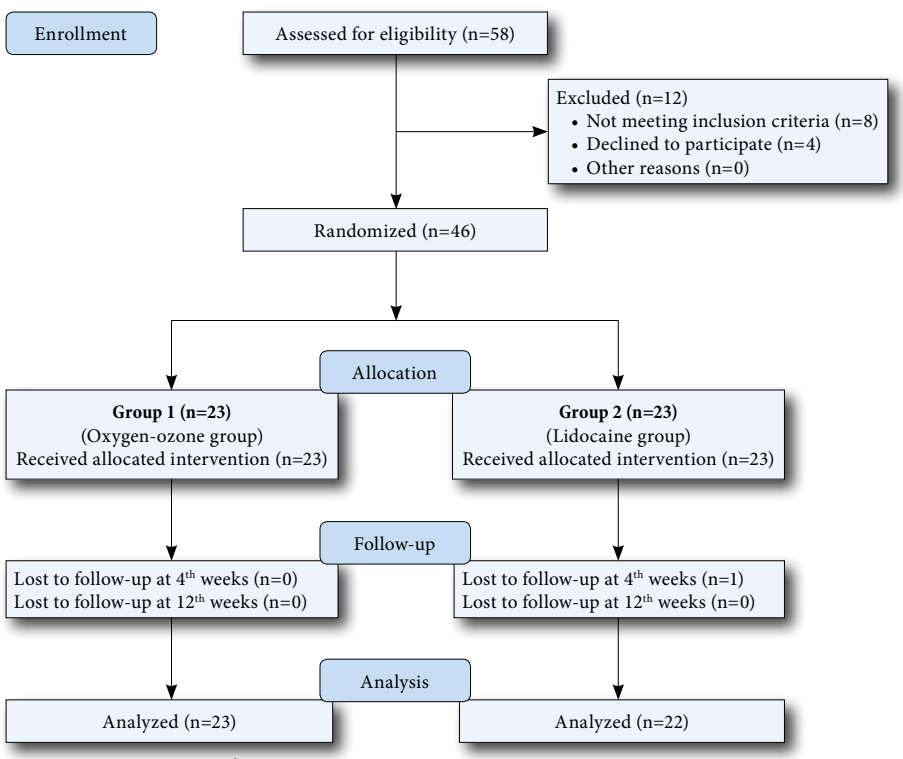

Figure 1. CONSORT diagram.

and pain triggered by fingertip pressure in the upper trapezius. Exclusion criteria were as follows: presence of cervical radiculopathy, cervical myelopathy, severe cervical discal or bony degeneration; history of neck trauma or surgery in the past year; trigger point injection to the trapezius within the last three months; cognitive impairment, fibromyalgia, inflammatory disease such as rheumatoid arthritis, polyneuropathy, coagulopathy, malignant hypertension, Graves' disease, severe thrombocytopenia (platelet count <50,000/μL), and pregnancy. Finally, of a total of 59 patients who were screened initially, 46 (8 males, 38 females; mean age: 44.7±10.4 years; range, 25 to 65 years) were included. The CONSORT diagram is shown in Figure 1.

Baseline demographics such as age, sex, and dominant side and clinical features such as symptomatic side and duration of symptoms of all patients were recorded.

Randomization

The patients were randomly divided into two groups: oxygen-ozone injection group (n=23) and lidocaine injection group (n=23). A randomized table of numbers obtained from a computer program, which was formed by an independent person who did not recruit and treat the patients, were used for randomization. A single physiatrist performed treatment of the patients as oxygen-ozone or lidocaine injection, according to the order in the table, and another single physiatrist who was blinded to the injection method recruited and followed up all patients.

Interventions

Trigger point in the upper trapezius muscle were determined by manual palpation. The most painful trigger point was marked with a skin marker. All interventions were performed in the sitting upright position. The location of trigger point was recorded for the next sessions according to their distance from certain anatomical landmarks. If the trigger point was activated at a different point during the examination, no injection was made, the second and third injections were performed to the first trigger point. Then, the injection site was cleaned using the appropriate antiseptic solution. Trigger point was caught between thumb and index finger and the injection was performed with a 40-mm long 27-gauge needle. The needle was inserted to the skin at a 90-degree angle and moved, until it arrived the trigger point. All injections were administered once a week for three consecutive weeks by a single physiatrist with 10-year experience in musculoskeletal practice.

Oxygen-ozone mixture (5 mL) with an ozone concentration of 10 μg/mL obtained using an ozone generator (Evozone GmbH, Reutlingen, Germany) was injected to patients in the oxygen-ozone injection group. In the lidocaine injection group, a total of 2 mL of 1% lidocaine that is the same amount as in the study of Ay et al.[19] was injected to the marked trigger point.

The patients were asked to report any side effects at each assessment. Participants in both groups were informed about an exercise program which included trapezius stretching, posture and relaxation exercises, and were asked to continue the exercises during follow-up.

Outcome measurements

The participants' response to the injections was measured with the four-outcome measurements. All assessments were performed before treatment, at four and 12 weeks after the last injection by a single physiatrist who was blinded to the injection method. The primary outcome measure of the study was pain severity evaluated with Visual Analog Scale (VAS). It is a 10-point scale in which 0 indicates no pain and 10 indicates the worst pain. Secondary outcome measures were active cervical lateral flexion range of motion (ROM), pain score (PS), and Neck Disability Index (NDI).

For the measurement of active cervical lateral flexion ROM, the patients were asked to bend their neck to the right and left side in sitting position. The measurements were made using a goniometer for three times and the highest values in both directions were averaged. Normal lateral flexion from the origin on both sides is 45°.[20]

To assess the severity of pain, PS measurement was performed by placing the thumb on the trigger point and applying pressure, until the nail bed turned white. Scores were made as 0 "no pain", 1 "mild pain", 2 "significant pain", and 3 "severe pain" leading to jumping sign.

The NDI was used to evaluate functional disability caused by neck pain. It consists of 10 questions defining the impact of pain on different activities such as reading, driving, sleeping, etc. Each question is graded from 0 (stating no functional limitation due to pain) to 5 (stating that an activity is impossible to perform). The total score ranges

from 0 to 50, with higher scores indicating more pain and disability.[21] Its adapted and validated version in Turkish was used.[22]

Statistical analysis

Study power and sample size calculation were performed using the G*Power version 3.1 software (Heinrich Heine Universität Düsseldorf, Düsseldorf, Germany). It was assigned that, based on the study of Ata et al.,[23] the minimum number of patients for each group was 21, with 80% power and 5% type 1 error probability. Considering the 10% probability of dropout during the study, it was planned to include a total of 46 patients, 23 for each group.

Statistical analysis was performed using the IBM SPSS version 15.0 software (SPSS Inc., Chicago, IL, USA). Continuous data were expressed in mean ± standard deviation (SD) and median and interquartile range (IQR), while categorical data were expressed in number and frequency. A non-significant Shapiro-Wilk test was used to determine whether the obtained parameters were appropriate for normal distribution. As the parameters were not normal, non-parametric analysis was used for comparisons. The chi-square test was applied to comparisons of categorical variables, and the Mann-Whitney U test or independent samples t-test for comparison of the changes in outcome measures between the groups. Repeated-measure analysis of variance (ANOVA; two-way) was used for the comparison of differences across different time points within groups and between groups. Post-hoc analysis was conducted with the Wilcoxon signed-rank test with a Bonferroni correction. A p value of <0.05 was considered statistically significant.

RESULTS

Of a total of 46 patients included in the study, one from the lidocaine group was lost to follow-up. As a result, 45 patients completed the three-week intervention and 12-week follow-up period and the data of these patients were analyzed. There was no significant difference in the baseline demographic and clinical characteristics between the groups (Table 1).

Based on repeated measurement analysis of variance, a significant effect of time was determined for VAS, PS, and NDI in both groups (Table 2). Compared to baseline versus Weeks 4 and 12, the VAS, PS, and NDI scores significantly decreased over time in the oxygen-ozone and lidocaine groups (p<0.001 for all). However, the change between the ROM measurements over time was not statistically significant between the groups (p>0.05 for all). There was no significant

TABLE 1
Baseline demographic and clinical characteristics of the patients

	Oxygen-ozone (n=23)					Lidocaine (n=22)					
Parameters	n	%	Mean±SD	Median	IQR	n	%	Mean±SD	Median	IQR	*p*
Age (year)			43.8±8.7	44.00	26.00-57.00			46.1±11.9	48.5	25.00-65.00	0.420
Sex											0.396
Male	3	13				5	22.7				
Female	20	87				17	77.3				
Employment											0.100
Employed	14	60.9				8	36.4				
Unemployed	9	39.1				14	63.6				
Dominant side											0.109
Right	23	100				19	86.4				
Left	0	0				3	13.6				
Symptomatic side											0.672
Right	15	65.2				13	59.1				
Left	8	34.8				9	40.9				
Symptoms duration (months)			62.6±65.2	24.00	3.00-228.00			31.5±33.3	15.00	3.00-120.00	0.093
VAS (0-10)			8.3±1.5	8.00	5.00-10.00			7.7±1.2	8.00	4.00-10.00	0.086
ROM (0-45)			43.3±3.5	45.00	30.00-45.00			43.9±3.8	45.00	30.00-45.00	0.189
Pain score (0-3)			2.7±0.5	3.00	2.00-3.00			2.7±0.5	3.00	2.00-3.00	0.921
Neck Disability Index (0-50)			19.3±7.4	17.00	8.00-37.00			16.8±9.1	15.00	5.00-37.00	0.270

SD: Standard deviation; IQR: Interquartile range; VAS: Visual Analog Scale; ROM: Range of motion.

TABLE 2
Summary of findings for outcome measures

	Score			Within-group change score						Repeated measure ANOVA			
	Baseline	4 weeks	12 weeks	Baseline *vs.* 4 weeks		Baseline *vs.* 12 weeks		4 weeks *vs.* 12 weeks		Time		Time* group	
	Mean±SD	Mean±SD	Mean±SD	Mean	95% CI	Mean	95% CI	Mean	95% CI	*F*	*p*	*F*	*p*
Visual Analog Scale													
Oxygen-ozone	8.34±1.46	5.08±2.67	5.21±2.76	3.26*	2.07-4.51	3.00*	1.66-4.33	-0.26	-1.45-0.93	74.02	<0.001*	3.71	0.028*
Lidocaine	7.72±1.16	3.36±2.30	2.40±2.38	4.00*	2.71-5.28	4.95*	3.59-6.31	0.95	-0.26-2.17				
Range of motion													
Oxygen-ozone	43.34±3.51	44.26±1.73	44.78±1.04	-0.91	-2.15-0.33	-1.43	-2.97-0.10	-0.52	-1.06-0.02	5.25	0.071	0.64	0.258
Lidocaine	43.86±3.75	44.54±1.47	44.54±1.47	-0.68	-1.95-0.59	-0.68	-2.25-0.89	0.00	-0.56-0.56				
Pain score													
Oxygen-ozone	2.69±0.47	1.39±0.94	1.52±0.94	1.30*	0.81-1.79	1.17*	0.64-1.70	-0.13	-0.51-0.25	70.35	<0.001*	1.50	0.226
Lidocaine	2.68±0.47	1.22±0.97	1.04±0.99	1.45*	0.95-1.95	1.63*	1.09-2.17	0.18	-0.21-0.57				
Neck Disability Index													
Oxygen-ozone	19.30±7.40	12.69±7.25	11.60±7.02	6.60*	2.43-10.78	7.69*	3.55-11.84	1.08	-1.15-3.33	36.40	<0.001*	0.21	0.805
Lidocaine	16.77±9.13	9.72±6.83	7.72±5.64	7.04*	2.78-11.31	9.04*	4.80-13.28	2.00	-0.29-4.29				

ANOVA: Analysis of variance; SD: Standard deviation; * p<0.05.

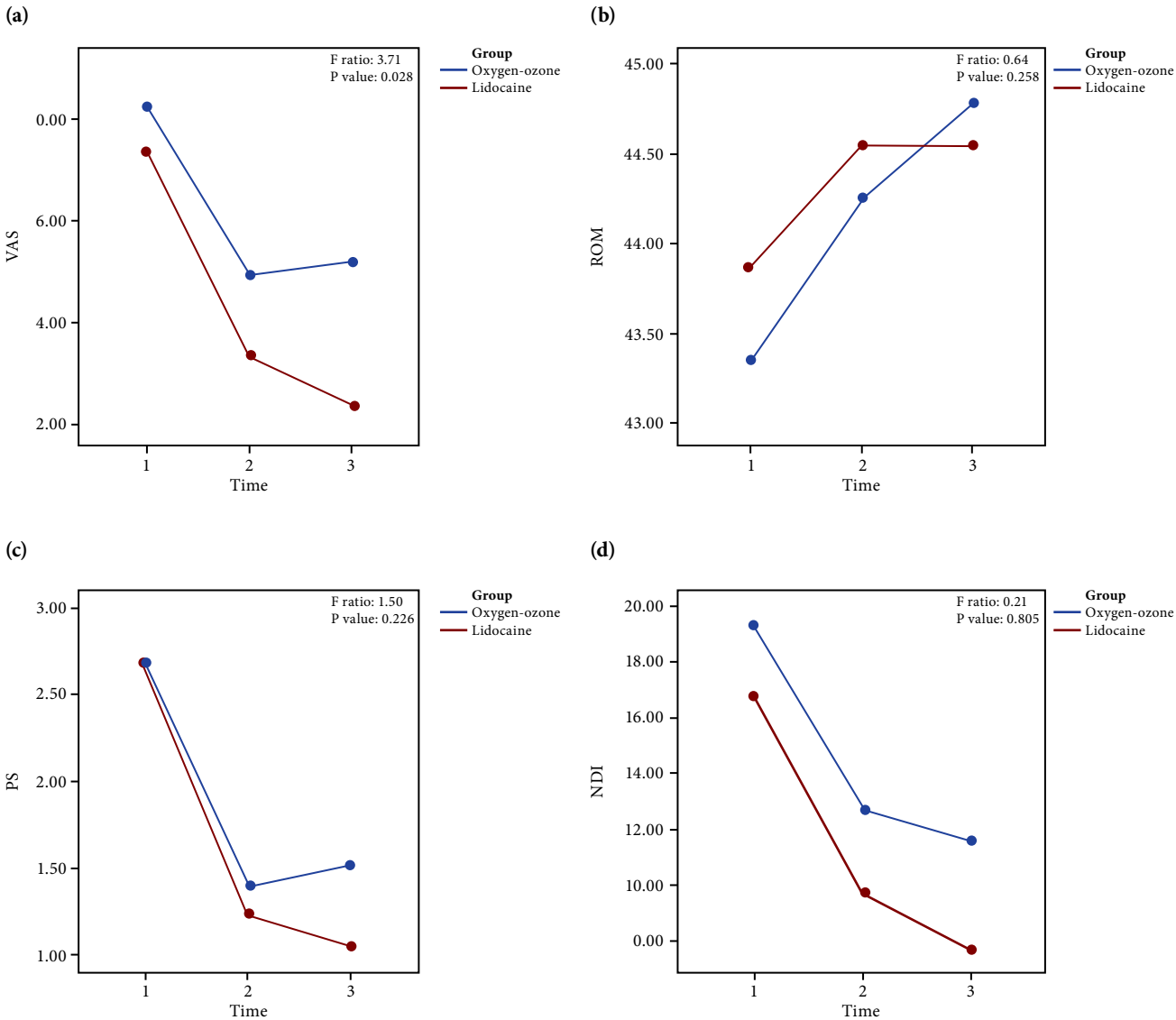

Figure 2. Change of the outcome measures over time in oxygen-ozone and lidocaine groups based on the repeated-measure analysis of variance (estimated marginal means are shown). **(a)** Visual Analog Scale (VAS); **(b)** Range of motion (ROM); **(c)** Pain score (PS); **(d)** Neck disability index (NDI). Time: 1, Baseline; 2, Week 4; 3, Week 12.

change in all outcome measurements in both groups at Week 12 compared to Week 4 ($p>0.05$ for all). Figure 2 depicts change of the outcome measures over time in both groups. A significant group × time interaction was detected regarding the VAS scores ($p=0.028$). However, no significant group × time interaction was identified regarding the ROM, PS, and NDI scores ($p>0.05$ for all).

DISCUSSION

In the present study, we investigated the efficacy of oxygen-ozone injections based on ROM, pain, and functional assessment tools during 12-week follow-up in patients with MPS and also compared the effectiveness of oxygen-ozone and lidocaine injections. Our study findings suggested that both oxygen-ozone and lidocaine injections applied to the trigger point were effective in improving pain and function in MPS. In addition, the improvement in pain over time was significantly higher with the lidocaine injection than with the oxygen-ozone injection. However, there was no significant difference in the improvement between the two groups, except for that the pain was more reduced in the lidocaine group.

In the literature, the effectiveness of lidocaine injection on trigger point in patients with MPS has been shown in many studies.[7-9,19] The efficacy of other injection methods applied to the trigger point in the treatment of MPS has been frequently compared with lidocaine.[7,9,19,24,25] Ay et al.[19] compared lidocaine injection with dry needling and reported that both methods were effective in improving pain, ROM, and mood. Kamanli et al.[7] compared lidocaine, botulinum toxin and dry needling, and all groups showed favorable results; however, lidocaine showed superiority in some pain parameters. In addition, the effectiveness of lidocaine was compared with 0.9% saline solution,[9] granisetron,[24] and acupuncture,[25] and lidocaine was either more effective,[24] or the efficacy profile was similar.[9,25] Since lidocaine trigger point injection is an effective and common method in the treatment of MPS patients, we compared the effect of oxygen-ozone trigger point injection versus lidocaine in this study.

Recently, several studies have demonstrated the benefits of using oxygen-ozone injection on symptoms and signs in the treatment of musculoskeletal diseases.[14-17] However, so far, the efficacy of oxygen-ozone injection has been examined mainly in knee osteoarthritis,[15] and low back pain.[14] To the best of our knowledge, the evidence for the impact of oxygen-ozone injection to trigger point in patients with MPS is still limited. Raeissadat et al.[8] only evaluated the role of oxygen-ozone injection in the treatment of MPS patients with active trigger point in the upper trapezius muscle. They compared oxygen-ozone and lidocaine injections with dry needling and evaluated the efficacy of the injections at baseline and at four weeks after treatment. They reported that all three injections were effective, but dry needling was less effective than oxygen-ozone and lidocaine, and the effectiveness of oxygen-ozone and lidocaine was similar. The current study followed the patients longer for the assessment of the efficacy of oxygen-ozone and lidocaine injections to trigger point in patients with MPS and demonstrated that both injections effectively improved pain and functional status at four and 12 weeks after treatment. As in the aforementioned study,[8] we showed that oxygen-ozone and lidocaine injections were similarly effective in improving NDI and some PS. However, unlike the previous study,[8] lidocaine injection was more effective than oxygen-ozone injection in improving VAS measures in our study. This difference may be due to the lower baseline VAS scores and closer proximity between groups in the study of Raissedat et al.[8] In addition, although it was not statistically significant, it may be due to the higher baseline VAS values scores of the oxygen-ozone group than lidocaine group in this study.

In the literature, several studies have shown that cervical ROM improved in some directions and at some follow-up time points after lidocaine injection.[8,9,11,19] However, in this study, there was no significant change in ROM within and between the groups over time. This may be due to the fact that cervical lateral flexion ROM values in the study were close to the normal cervical ROM value.[20] Although it is difficult to find cases with pure MPS in patients with neck pain,[26] we attempted to include individuals with MPS without significant discal and bony degenerations in this study. Indeed, the baseline ROM values were close to normal values, suggesting that patient selection was appropriate. In addition, baseline NDI scores of both groups in this study were below 20, supporting the suitability of patient selection.

Despite its significant effect on public health, there is no definitive understanding of the mechanism of the trigger point.[27] This is probably due to complex pathogenesis of the disorder, that includes the neuromuscular inputs, integration of cellular signaling, local circulation, excitation-contraction coupling, and energy metabolism. In addition, some authors have hypothesized that microtubule density and calcium are elevated in the trigger point region and reactive oxygen species act as a disease modifier for the formation of trigger point in MPS.[27] Ozone, with its anti-inflammatory, antioxidant, and immunomodulatory effect, which has been suggested for the last four decades, may have been effective on trigger point.[14] In addition, as proposed by Simon and Travell,[28] it may have contributed to trigger point inactivation by the mechanical effects on muscle fibers.

In previous studies, the concentration and volume of oxygen-ozone injected in the treatment of musculoskeletal disorders vary and there is no single protocol.[29] Raeissadat et al.[8] injected 8 mL of oxygen-ozone with an ozone concentration of 15 μg/mL into the trigger point in the treatment of MPS. In this study, a 5 mL of oxygen-ozone session at a concentration of 10 μg/mL recommended by the International Scientific Community of Ozone Therapy (ISCO3)[30] was used. No side effects were observed in either group.

Nonetheless, the current study has some limitations. First, the patients were not blinded to the injection method, which could be a potential cause of bias. The absence of a sham or placebo group was another limitation. Therefore, the placebo effect and spontaneous recovery effect could not be excluded. Third, only lateral flexion was evaluated as a ROM measurement. Indeed, it was not intended to create data complexity by evaluating the ROM from all aspects. Instead, we preferred to evaluate PS and functionality together with pain severity as outcome measures. The fourth limitation is that the pain threshold level of the participants was unable to be evaluated. The main strength of this study is, however, that it has a prospective, well-designed nature, the researcher who evaluated the patients was blind to the injection method, and the study has a 12-week follow-up period.

In conclusion, oxygen-ozone and lidocaine injections of the trigger point can effectively improve pain and functional status at four and 12 weeks after treatment in patients with MPS. However, lidocaine injection appears to be superior in reducing pain compared to oxygen-ozone injection, although it is not superior to in improving function and PS. To the best of our knowledge, the current study is the first comparing the efficacy of oxygen-ozone and lidocaine injections to the trigger point in MPS with a 12-week follow-up. On the other hand, further large-scale and long-term prospective, randomized clinical studies including placebo groups are warranted to confirm these findings.

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Ethics Committee Approval: The study protocol was approved by the Düzce University Getat Ethics Committee (date: 30.12.2020, no: 2020-7-4). This study was registered at the US National Institutes of Health (ClinicalTrials.gov) database (NCT04885881). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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