



## Clinical Research Article

# Comparison of ultrasound-guided subacromial corticosteroid and ozone (O<sub>2</sub>-O<sub>3</sub>) injections in the treatment of chronic rotator cuff tendinopathy: a randomized clinical trial

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## ABSTRACT

**Background:** The authors aimed to compare the effects of a one-time ultrasound (US)-guided subacromial corticosteroid injection and three-time ozone (O<sub>2</sub>-O<sub>3</sub>) injection in patients with chronic supraspinatus tendinopathy.

**Methods:** Participants were randomly assigned to the corticosteroid group (n = 22) or ozone group (n = 22). Injections in both groups were administered into subacromial bursa with an US-guided in-plane posterolateral approach. Primary outcome measure was the change in the Western Ontario Rotator Cuff Index (WORC) score between baseline and 12-weeks post-injection. Secondary outcome measures included visual analog scale and Shoulder Pain and Disability Index scores. Assessments were recorded at baseline, and 4-weeks and 12-weeks post-injection.

**Results:** Forty participants completed this study. Based on repeated measurement analysis of variance, a significant effect of time was found for all outcome measures in both groups. Both the groups showed clinically significant improvements in shoulder pain, quality of life, and function. Baseline, 4-week post-injection, and 12-week post-injection WORC scores (mean ± standard deviation) were 57.91 ± 18.97, 39.10 ± 20.50 and 37.22 ± 27.31 in the corticosteroid group, respectively and 69.03 ± 15.89, 39.11 ± 24.36, and 32.26 ± 24.58 in the ozone group, respectively. However, no significant group × time interaction was identified regarding all outcome measures.

**Conclusions:** Three-time ozone injection was not superior to a one-time corticosteroid injection in patients with chronic supraspinatus tendinopathy. It might be as effective as corticosteroid injection at 4-weeks and 12-weeks post-injection in terms of relieving pain and improving quality of life and function.

**Keywords:** Adrenal Cortex Hormones; Bursa, Synovial; Ozone; Pain Management; Rotator Cuff; Shoulder Pain; Steroids; Tendinopathy; Ultrasonography, Interventional.

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## INTRODUCTION

Shoulder pain, the most frequent cause of which is rotator cuff tendinopathy (RCT), constitutes approximately 16% of all musculoskeletal symptoms [1,2]. RCT, which encompasses different shoulder conditions affecting subacromial structures such as subacromial bursitis, rotator cuff tendinosis/tendinitis, and shoulder impingement syndrome, is a chronic overuse or degenerative disorder without active inflammation [2-5].

Conservative treatment of RCT includes exercise therapy, nonsteroidal anti-inflammatory drugs, physical therapy modalities, and injections such as corticosteroid and platelet-rich plasma [6-8]. To improve motion and decrease pain in all stages of RCT, corticosteroid injections are often preferred as a low-cost and effective management option [9]. Nonetheless, the short-term efficacy of the corticosteroid injection has been demonstrated [10]. Corticosteroid injections can also cause tendon failure and collagen synthesis inhibition [11].

Ozone ( $O_3$ ), consisting of 3 oxygen atoms, is an inorganic molecule with allotrope features. It is found in the stratosphere in nature, and it can also be formed artificially by exposure to a high-voltage electric current. Currently, a medical mixture consisting of  $O_2$  and  $O_3$  is formed by a medical generator by passing pure  $O_2$  over a high-voltage gradient [12]. The use of ozone therapy ( $O_2$ - $O_3$ ) in musculoskeletal disorders has increased in recent years. Ozone ( $O_2$ - $O_3$ ) may assist in decreasing inflammation and pain by blocking phosphodiesterase-A2 and downregulating tumor necrosis factor alpha and TNFR2 [13]. Other beneficial effects of ozone ( $O_2$ - $O_3$ ) in the body include increased blood flow and fibroblastic activity and starting the repair process at the tissue level [14,15]. With the use of ozone ( $O_2$ - $O_3$ ), no allergic side effects or destructive effects on cartilage or tendons have been noted [16].

To the authors' knowledge, there is only one study in the literature comparing the efficacy of corticosteroid and ozone ( $O_2$ - $O_3$ ) injections in the management of shoulder disorders [17]. The study, conducted in patients with shoulder impingement syndrome, demonstrated that a one-time corticosteroid injection provided more significant improvement in disability and pain scores than a one-time ozone injection [17]. The authors hypothesized that three-time ozone injection would improve pain, function, and quality of life more than a one-time steroid injection. Therefore, the aim was to compare the effects of ultrasound (US)-guided subacromial a one-time corticosteroid and three-time ozone ( $O_2$ - $O_3$ ) injection in pa-

tients with chronic supraspinatus tendinopathy.

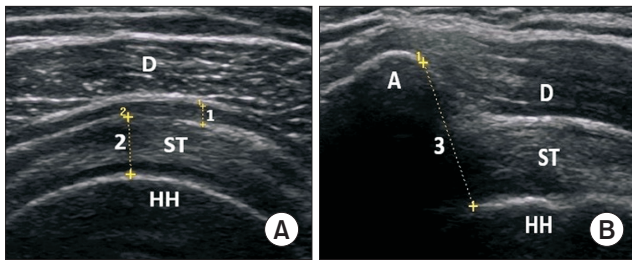
## MATERIALS AND METHODS

### 1. Study design and participants

The design of this study was a single-center, prospective, randomized clinical trial. The study was performed from January to May 2022 on patients with chronic supraspinatus tendinopathy admitted to the physical medicine and rehabilitation outpatient clinics of a tertiary hospital. Inclusion criteria were as follows: (1) aged between 18 and 70 years, (2) rotator cuff tendinosis or partial rotator cuff tear only on the supraspinatus tendon diagnosed by US or magnetic resonance imaging (MRI), (3) chronic pain in the shoulder region for more than 3 months and an increase in pain with overhead-throwing activity. Exclusion criteria were as follows: (1) a full-thickness rotator cuff tear diagnosed by US or MRI, (2) subacromial/intra-articular injections in the last 3 months, (3) contraindications of ozone ( $O_2$ - $O_3$ ) injection, such as pregnancy, platelet level  $< 50 \times 10^3/\mu\text{L}$ , glucose-6 phosphate dehydrogenase deficiency, and uncontrolled hyperthyroidism (4) allergic reaction to betamethasone or lidocaine, (5) history of hepatitis, coagulopathy, or diabetes (6) history of tumor, trauma, shoulder infection, bony lesion, inflammatory rheumatic diseases, or fracture, and (7) history of brachial plexus lesion/cervical radiculopathy. Participants were not allowed to take any topical or oral analgesics for pain during the study. The study protocol and design were approved by the local Ethics Committee (approval number: E-95961207-604.01.01-6296). Clinicaltrials.gov database registration (NCT05207384) was performed for this study. To participate the study, all participants gave written informed consent.

### 2. Randomization and blinding

Participants were randomly assigned to the intervention groups using a computer-generated list of numbers by one of the researchers who did not make the assessment of the participants. Outcome measures were assessed by an independent physiatrist, blinded for the assigned treatment. The participants and the injecting physiatrist were not blinded to group allocation due to the interventions' nature (liquid versus gas). The participants were briefed not to disclose group treatment allocation throughout assessments.



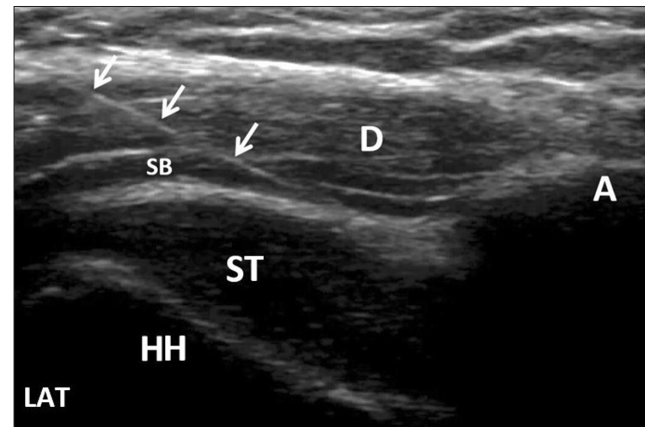
**Fig. 1.** (A) Measurement of the thicknesses of the subacromial bursa (1) and supraspinatus tendon (2). (B) Measurement of the acromiohumeral distance (3). A: acromion, D: deltoid, HH: humeral head, ST: supraspinatus tendon.

### 3. Baseline assessment

Participants' characteristics including age, sex, dominant hand, duration of symptoms, affected shoulder, and ultrasonographic features were recorded at baseline. Subacromial bursa thickness, acromiohumeral distance, and supraspinatus tendon thickness were measured by US in both groups with the shoulder in internal rotation. The thicknesses of the subacromial bursa and supraspinatus tendon were measured in the short-axis view. Measurements were taken from the thickest part of the supraspinatus tendon and the greatest fluid thickness of the subacromial bursa (**Fig. 1**). Acromiohumeral distance was measured by positioning the transducer on the lateral surface of the acromion's anterior aspect along the humerus' longitudinal axis and defined as the distance between the acromion and humeral head (**Fig. 1**). Symptoms of participants were assessed with the Western Ontario Rotator Cuff Index (WORC), visual analog scale (VAS) and Shoulder Pain and Disability Index (SPADI).

### 4. Interventions

Injections in both groups were performed by the same physiatrist under US guidance (with a 5–12 MHz linear transducer [Logic e portable; GE Healthcare, Jiangsu, China]) and administered into the subacromial bursa with an in-plane posterolateral approach (**Fig. 2**). A mixture of 1 mL corticosteroid (betamethasone 3 mg/mL) and 1 mL lidocaine (20 mg) were injected using a 27-G needle in the corticosteroid injection group. Three sessions (1 session/week) of 5 mL of ozone ( $O_2-O_3$ ) (with a concentration of 10  $\mu\text{g}/\text{mL}$  in the first session, 15  $\mu\text{g}/\text{mL}$  in the second session, and 20  $\mu\text{g}/\text{mL}$  in the third session) were injected using a 27-G needle in the ozone ( $O_2-O_3$ ) injection group. The ozone ( $O_2-O_3$ ) injectate was prepared using a medical ozone generator (EVOZONE,



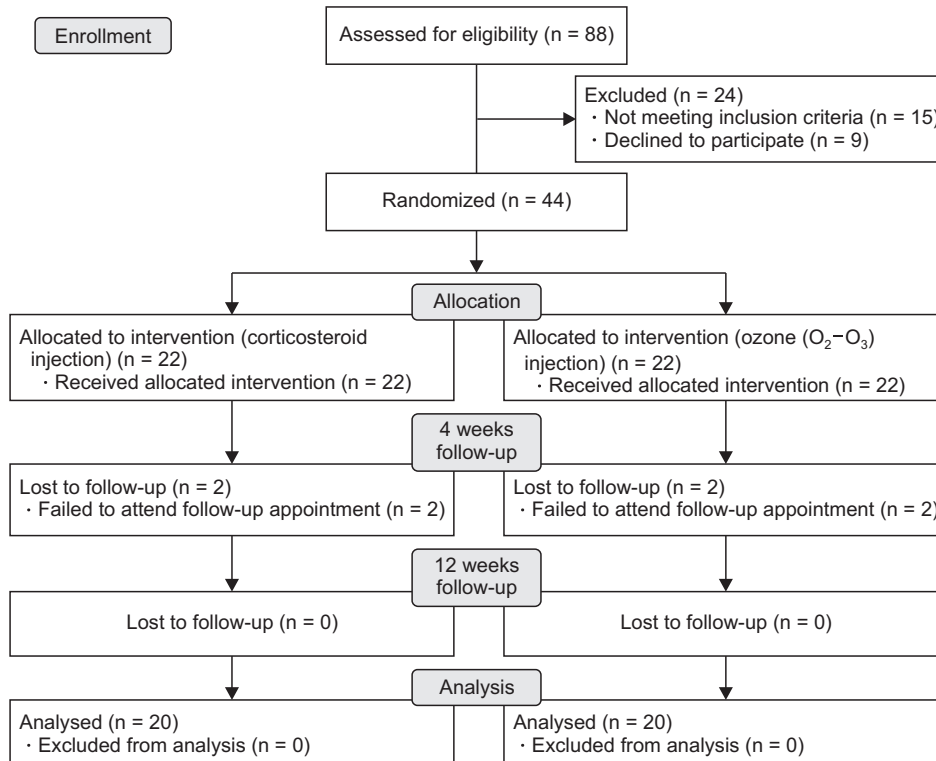
**Fig. 2.** Ultrasound-guided subacromial bursa injection with an in-plane posterolateral approach. Arrows: needle, A: acromion, D: deltoid, HH: humeral head, ST: supraspinatus tendon, SB: subacromial bursa, LAT: lateral.

Reutlingen, Germany). The determined ozone ( $O_2-O_3$ ) concentration was chosen, and a 5 mL volume of ozone ( $O_2-O_3$ ) was filled into the syringe from the generator. It was recommended that all participants perform shoulder range of motion exercises, stretching, and strengthening exercises daily.

### 5. Outcome measures

The primary outcome measure was the change in the WORC score between the baseline and 12-weeks post-injection. Secondary outcome measures included the SPADI and VAS scores. Assessments were recorded at baseline, and at 4-weeks and 12-weeks post-injection. In the ozone ( $O_2-O_3$ ) group, assessments were performed on the 4th week and 12th week after completion of 3 injection sessions. Participants were asked to report any side effects at each assessment. A self-administered evaluation tool, the WORC, has been used for RCT [18]. The WORC evaluates the disease-specific quality of life and upper-extremity function [18,19]. There are 21 questions in total for 5 different domains that evaluate physical symptoms, work, emotional well-being, social well-being, and sports and recreation. A score of 100-mm is applied to each question and higher scores correspond to greater problems. The validity of the WORC for use in Turkish has been shown [18]. The hundred-point VAS (from 0 [no pain] to 100 [worst pain imaginable]) was used for assessment of shoulder pain severity in the last week.

The SPADI, a self-assessment questionnaire with 13 questions, has been applied to measure pain (5 questions) and disability (8 questions) [20]. For each question,



**Fig. 3.** CONSORT diagram of the study.

a scale varying from 0 to 100 is used in that and higher scores correspond to greater pain and disability.

## 6. Statistical analysis

The sample size was estimated by means of the G\*power (V3.1) program. To achieve a power of 80% with 5% probability of type 1 error and detect a clinically significant 17% difference in the WORC score between the 2 groups, the identified sample size was 18 patients per group based on the study by Ekeberg et al. [21]. Considering the 20% probability of patient loss during the study, a total of 44 patients were planned to be included in the study.

SPSS Statistics v15.0 (SPSS Inc., Chicago, IL) was used for statistical analysis. A nonsignificant Shapiro-Wilk test showed the data distribution's normality. Continuous data were demonstrated as the mean  $\pm$  standard deviation and median (interquartile range). Percentages were given for categorical data. Nominal data analysis was conducted using the Pearson  $\chi^2$  test. Mann-Whitney *U*-test or independent samples *t*-test were used for comparing two groups. Since WORC, the primary outcome, was normally distributed, comparison was made using the independent samples *t*-test. Repeated-measure analysis of variance (ANOVA; two-way) was used for comparison of differences across different time points within groups and

between groups, and post-hoc analysis was performed with the Bonferroni test. Statistical significance level was determined as  $P < 0.05$ .

## RESULTS

Sixty-eight patients were evaluated for study eligibility. Finally, 44 participants were randomly assigned to either the corticosteroid group or ozone ( $O_2-O_3$ ) group. After randomization, 4 patients, 2 in the corticosteroid group and 2 in the ozone ( $O_2-O_3$ ) group, were excluded from the study. The CONSORT diagram for participants was demonstrated in **Fig. 3**. There was no difference in demographic, ultrasonographic, or clinical features between the corticosteroid and ozone ( $O_2-O_3$ ) injection groups at baseline (**Table 1**).

Repeated-measure analysis of variance results were presented in **Table 2** and **Fig. 4**. A significant effect of time was detected for all outcome measures in both groups (**Table 2**). When baseline was compared to 4-weeks post-injection ( $P < 0.001$  for all outcome measures) and 12-weeks-post-injection ( $P < 0.001$  for all outcome measures), all outcome measures improved significantly over time in both groups (**Fig. 4**). No significant group  $\times$  time interaction was identified regarding the VAS ( $P = 0.146$ ),

**Table 1.** Demographic and clinical features of the corticosteroid and ozone (O<sub>2</sub>-O<sub>3</sub>) groups at baseline

Parameters	Corticosteroid group (n = 20)	Ozone (O <sub>2</sub> -O <sub>3</sub> ) group (n = 20)	P value
Age (yr)	50.15 ± 12.75 (51.00 [37.25/61.75])	48.20 ± 10.38 (49.00 [42.25/56.00])	0.599
Sex			0.110
Female	9 (45.0)	14 (70.0)	
Male	11 (55.0)	6 (30.0)	
Duration of symptoms (mo)	13.80 ± 23.22 (4.00 [4.00/11.00])	21.35 ± 25.60 (9.50 [4.50/24.00])	0.335
Right-handed	19 (95.0)	16 (80.0)	0.151
Dominant shoulder affected	13 (65.0)	11 (55.0)	0.519
Subacromial bursa thickness (mm)	0.13 ± 0.05 (0.13 [0.08/0.16])	0.10 ± 0.06 (0.10 [0.07/0.14])	0.239
Supraspinatus thickness (mm)	0.58 ± 0.09 (0.56 [0.50/0.65])	0.60 ± 0.11 (0.62 [0.52/0.67])	0.436
Acromiohumeral distance (mm)	1.41 ± 0.28 (1.41 [1.18/1.65])	1.36 ± 0.19 (1.35 [1.27/1.46])	0.551
VAS (0–100)	65.25 ± 15.85 (60.00 [50.00/80.00])	75.50 ± 17.00 (80.00 [70.00/87.50])	0.056
WORC (0–100)	57.91 ± 18.97 (58.05 [48.60/73.65])	69.03 ± 15.89 (68.10 [59.40/83.47])	0.052
SPADI (0–100)	62.00 ± 19.24 (61.90 [47.70/77.52])	65.38 ± 16.22 (65.35 [51.55/78.50])	0.551

Data were shown as mean ± standard deviation (median [interquartile range]).

VAS: visual analog scale, WORC: The Western Ontario Rotator Cuff Index, SPADI: Shoulder Pain and Disability Index.

WORC ( $P = 0.071$ ), and SPADI ( $P = 0.766$ ) scores (**Table 2**, **Fig. 4**). The patients did not report any adverse effects in either group.

## DISCUSSION

The current study aimed to compare the effects of US-guided subacromial corticosteroid and ozone (O<sub>2</sub>-O<sub>3</sub>) injection in patients with chronic supraspinatus tendinopathy. The findings of this study showed that both corticosteroid and ozone (O<sub>2</sub>-O<sub>3</sub>) injection yielded clinically significant improvements in shoulder pain, quality of life, and function. However, no significant difference was identified between a one-time corticosteroid injection and three-time ozone (O<sub>2</sub>-O<sub>3</sub>) injection.

Ozone (O<sub>2</sub>-O<sub>3</sub>) therapy has been used for treatment of various diseases since the last century. Ozone (O<sub>2</sub>-O<sub>3</sub>) injection has been demonstrated to be beneficial in the treatment of diseases such as plantar fasciitis, knee osteoarthritis, and cervical and lumbar spine pathologies [16,17,22].

There are a limited number of studies investigating the effectiveness of ozone (O<sub>2</sub>-O<sub>3</sub>) therapy in shoulder disorders [17,23,24], and the studies differ from each other in terms of the concentration and volume of injected ozone (O<sub>2</sub>-O<sub>3</sub>), the number of injection sessions, and the injection technique.

In a randomized controlled study performed on patients with shoulder impingement syndrome by Babaei-Ghazani et al. [17], corticosteroid injection was shown

to improve disability and pain scores better than ozone (O<sub>2</sub>-O<sub>3</sub>) injection. In that study, unlike the present study, a session of 8 mL of ozone (O<sub>2</sub>-O<sub>3</sub>) at a concentration of 12 µg/mL was administered into the subacromial bursa with an in-plane lateral to medial approach. The difference in the results of the present study compared to that study may be related to the repeated ozone injections at specified intervals. Repetition of ozone (O<sub>2</sub>-O<sub>3</sub>) injections at specified intervals may be required for long-term clinical improvement and continued efficacy. In tendinopathies, the International Scientific Community of Ozone Therapy (ISCO3) recommends starting with a concentration of 10 µg/mL and increasing the concentration to 20 µg/mL, if possible, in the second or third injection [25]. The ISCO3 also recommends the use of more suitable and the thinnest needle for the injection, that 5–10 mL of ozone can be injected into the shoulder tendons depending on the affected tendons, and that injections should be performed once a week up to 3–5 times [25]. Even if it might be regarded as a bias which is a limitation in the research protocol, a series of three ozone (O<sub>2</sub>-O<sub>3</sub>) injections was preferred in the present study.

The efficacy of ozone (O<sub>2</sub>-O<sub>3</sub>) injection has been demonstrated in two studies conducted in patients with RCT, involving different injection techniques and different number of sessions than ours. In these studies, similar to the present study, ozone (O<sub>2</sub>-O<sub>3</sub>) injections were performed with repeated doses at specified intervals.

In the first study conducted by Scarchilli [24] on patients with RCT, 5 sessions of 10 mL ozone (O<sub>2</sub>-O<sub>3</sub>) injection at a concentration of 10 µg/mL were performed at

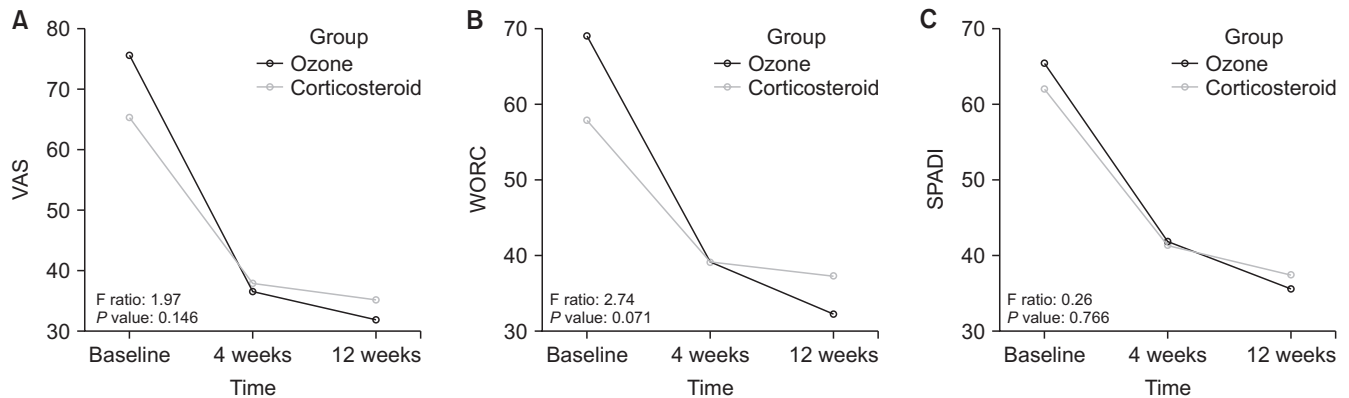
**Table 2.** Summary of findings for outcome measures

Outcome measures	Score			Within-group change score			Repeated measure ANOVA F (P)	
	Baseline	4 weeks	12 weeks	Baseline vs. 4 weeks	Baseline vs. 12 weeks	4 weeks vs. 12 weeks	Time	Time × Group
<b>VAS</b>								
Corticosteroid	65.25 ± 15.85	37.75 ± 21.79	35.00 ± 25.80	-27.50 (-40.12, -14.87)*	-30.25 (-44.64, -15.85)*	-2.75 (-14.52, 9.02)	61.78 (< 0.001)**	1.97 (0.146)
Ozone (O <sub>2</sub> -O <sub>3</sub> )	75.50 ± 17.00	36.50 ± 22.07	31.75 ± 26.42	-39.00 (-51.62, -26.37)*	-43.75 (-58.14, -29.35)*	-4.75 (-16.52, 7.02)		
<b>WORC</b>								
Corticosteroid	57.91 ± 18.97	39.10 ± 20.50	37.22 ± 27.31	-18.81 (-30.47, -7.14)*	-20.69 (-34.27, -7.10)*	-1.88 (-13.91, 10.15)	38.75 (< 0.001)**	2.74 (0.071)
Ozone (O <sub>2</sub> -O <sub>3</sub> )	69.03 ± 15.89	39.11 ± 24.36	32.26 ± 24.58	-29.91 (-41.57, -18.25)*	-36.77 (-50.35, -23.18)*	-6.85 (-18.89, 5.18)		
<b>SPADI</b>								
Corticosteroid	62.00 ± 19.24	41.31 ± 22.56	37.42 ± 26.63	-20.68 (-33.12, -8.24)*	-24.58 (-37.60, -11.49)*	-3.89 (-16.70, 8.91)	32.15 (< 0.001)**	0.26 (0.766)
Ozone (O <sub>2</sub> -O <sub>3</sub> )	65.38 ± 16.22	41.81 ± 26.54	35.53 ± 24.80	-23.57 (-36.01, -11.13)*	-29.85 (-42.94, -16.76)*	-6.27 (-19.08, 6.53)		

Data were shown as mean ± standard deviation or mean (95% confidence interval).

VAS: visual analog scale; WORC: The Western Ontario Rotator Cuff Index, SPADI: Shoulder Pain and Disability Index, ANOVA: analysis of variance.

\*P < 0.017; \*\*P < 0.05.



**Fig. 4.** Change of the outcome measures over time in corticosteroid and ozone ( $O_2-O_3$ ) groups based on the repeated-measure analysis of variance (estimated marginal means are shown). (A) Visual analog scale (VAS). (B) The Western Ontario Rotator Cuff Index (WORC). (C) Shoulder Pain and Disability Index (SPADI).

weekly intervals through posterior intra-articular access. In that study, it was shown that the effect of ozone ( $O_2-O_3$ ) injections on pain control continued for more than 2 months [24].

In the second study, Moretti et al. [23] conducted a prospective randomized study on patients with supraspinatus tendinosis and compared the effectiveness of anti-inflammatory mesotherapy and ozone ( $O_2-O_3$ ) injection. Six sessions of 10 mL of ozone ( $O_2-O_3$ ) with a concentration of 6- to 10- $\mu$ g were administered twice a week into the part with the most pain in the periarticular region. If shoulder osteoarthritis was accompanied, 10- to 15-mL of ozone ( $O_2-O_3$ ) with a concentration of 15- to 20- $\mu$ g was administered once a week intra-articularly. There was a greater decrease in VAS scores in the ozone ( $O_2-O_3$ ) group compared to the mesotherapy group [23].

In this study, no significant difference was detected between corticosteroid and ozone ( $O_2-O_3$ ) injection groups in terms of relieving pain and improving quality of life and function. Corticosteroid injection has already been shown to relieve pain and improve function in the short term [7]. The authors attribute the remarkable improvement in outcome measures in the ozone ( $O_2-O_3$ ) group to the favorable biological properties of the ozone ( $O_2-O_3$ ) molecule. Some possible effects of ozone ( $O_2-O_3$ ) therapy in the management of musculoskeletal diseases are the start of the repair process at the tissue level and increasing the analgesic and anti-inflammatory effects and tissue oxygenation by triggering the anti-nociceptive system [12,23,26]. The results of this study show that ozone ( $O_2-O_3$ ) injection can be considered as an alternative treatment to steroid injection in patients with supraspinatus tendinopathy. This indicates the clinical importance of the study. Considering that the follow-up period in this

study was 12 weeks, further studies with longer follow-ups and different outcome measures are needed to understand whether ozone ( $O_2-O_3$ ) is more effective than steroids in the long term.

Corticosteroid injection can cause skin hyperpigmentation or hypopigmentation, fat atrophy, and tendon rupture. Many animal models have demonstrated a decrease in rotator cuff tendon quality after corticosteroid injection [27,28]. On the contrary, ozone ( $O_2-O_3$ ) injection is a relatively safe and effective intervention. The safety of ozone ( $O_2-O_3$ ) injection has been shown in several studies [12,17,26]. To ensure safety, ozone ( $O_2-O_3$ ) concentrations should be set within a specific range [12]. In this study, ozone ( $O_2-O_3$ ) concentrations were determined by considering the concentrations recommended by the ISCO3 in tendinopathy [25]. Throughout the study, no patients experienced any adverse reactions to ozone ( $O_2-O_3$ ) injection, demonstrating that this substance was safe in therapeutic interventions as long as the concentrations were set within a specific range. Considering the side effects of the steroid and the lack of significant side effects of ozone ( $O_2-O_3$ ), the fact that ozone ( $O_2-O_3$ ) is as effective as the steroid in this study also shows that ozone ( $O_2-O_3$ ) can be alternative to steroids.

This study has some limitations. The absence of a real control group was the first limitation. It would be better to include one more group receiving no injection. The second limitation was that the injecting physiatrist and the participants could not be blinded due to the interventions' natures. The third limitation was that three-time ozone injection versus a one-time steroid injection and the injectate volume difference between the 2 groups can be considered a bias. The fourth limitation was the limited follow-up period. The last limitation of the study

was that the effect of ozone (O<sub>2</sub>-O<sub>3</sub>) injection on shoulder structures was not evaluated using an objective technique such as MRI.

In conclusion, the results of this study illustrate that three-time ozone (O<sub>2</sub>-O<sub>3</sub>) injection was not superior to a one-time corticosteroid injection in patients with chronic supraspinatus tendinopathy. It might be as effective as corticosteroid injection at 4-weeks and 12-weeks post-injection in terms of relieving pain and improving quality of life and function. Further studies with longer follow-ups are needed by involving another group having no injection.

## DATA AVAILABILITY

The datasets supporting the findings of this study are available from the corresponding author upon reasonable request.

## ACKNOWLEDGMENTS

We would like to thank the participants of the study.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

## FUNDING

No funding to declare.

## AUTHOR CONTRIBUTIONS

Merve Örucü Atar: Writing/manuscript preparation; Nurdan Korkmaz: Data curation; Sefa Gümrük Aslan: Study conception; Özge Tezen: Writing/manuscript preparation; Sinem Uyar Köylü: Investigation; Yasin Demir: Computation; Serdar Kesikburun: Study conception.

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