Clinical Rheumatology
https://doi.org/10.1007/s10067-018-4147-6

ORIGINAL ARTICLE

The effects of ultrasound-guided corticosteroid injection compared to oxygen–ozone (O_2–O_3) injection in patients with knee osteoarthritis: a randomized controlled trial

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Received: 15 February 2018 / Revised: 11 April 2018 / Accepted: 10 May 2018

Abstract

Osteoarthritis (OA) is a chronic multifactorial disease characterized by progressive joint degeneration. The purpose of this study was to compare the effects of ultrasound-guided corticosteroid injection with oxygen–ozone injection in patients with knee OA. This double-blind randomized clinical trial was performed on 62 patients with knee OA. The patients were randomly divided into two groups. In the first group 40 mg triamcinolone (1 cc) and in the second group 10 cc (15 μg/ml) oxygen–ozone (O_2–O_3) were injected into the knee joint under ultrasound guidance. Outcome measures included the Western Ontario and McMaster Universities Osteoarthritis (WOMAC), knee flexion range of motion (ROM), effusion in ultrasound images of the suprapatellar recess, and visual analog scale (VAS), which were evaluated before injection, 1 week, 1 month, and 3 months after the treatment. Sixty-two patients (10 men and 52 women) were enrolled with mean age of 57.9 years. VAS improved in both groups (steroid P value = 0.001, oxygen–ozone P value > 0.001). The improvements seen in VAS and WOMAC scores 3 months after treatment were in favor of the oxygen–ozone group when compared to the steroid group ($P = 0.041$ vs $P = 0.19$). There was no significant difference between the two groups in ROM and joint effusion seen under ultrasound (ROM $p = 0.880$, effusion $p = 0.362$). However, in the oxygen–ozone-receiving group, joint effusion was decreased significantly ($p < 0.001$). Both steroid and oxygen–ozone injections are effective in patients with knee osteoarthritis. Our study showed that the effects of oxygen–ozone injection last longer than those of steroid injection to the knee joint.

Keywords Corticosteroid · Knee · Osteoarthritis · Oxygen–ozone · Sonography

Introduction

Knee osteoarthritis (OA) is a degenerative condition that leads to the destruction, pain, deformity, and reduction in the function of involved joint [1]. The high prevalence of knee osteoarthritis, especially in the elderly population, has made it a costly task for health care providers [2]. At the age of 65 years old, approximately 11% of the population are symptomatic with radiological changes [3, 4]. The pain source in knee OA is from various joint elements, such as articular capsules, ligaments, synovial, bone, lateral part of menisci, tendons, and extra-articular ligaments [5, 6].

Total knee arthroplasty is a definite treatment for severe osteoarthritis. In younger patients, surgeons prefer to delay knee replacement due to the limited life of the prosthesis and possible complications related to revision surgeries. Non-surgical treatment options especially in mild to moderate conditions include physical therapy, anti-inflammatory drugs, exercise, intra-articular injections, and acupuncture [7, 8]. None of these treatment modalities are shown to have long-term effects in eliminating the pain and other symptoms related to the knee OA. Furthermore, none of these treatment modalities

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Published online: 24 May 2018

were shown superior to the others [4]. The intra-articular corticosteroid injection has been widely used to control the symptoms of OA. Since intra-articular corticosteroid injection can be done easily to reduce inflammation and pain especially with acceptable short-term efficacy, it is a temporary alternative option in order to try to postpone surgery [9, 10]. Frequent use of steroid injection should be avoided due to possible increased incidence of intra-articular infections and other adverse effects, such as degeneration of the articular cartilage [11, 12].

Recently, the therapeutic effects of oxygen–ozone injection were reported in management of different musculoskeletal disorders including low back pain, herniated disc, failed back syndrome, degenerative spine disease, and knee osteoarthritis [13–15]. There is limited evidence for oxygen–ozone application in patients with knee OA, and the exact mechanism of action is unknown. Several biological effects have been proposed to explain therapeutic effects of oxygen–ozone therapy. Increasing tissue oxygenation and anti-inflammatory and analgesic effects by stimulating the anti-nociceptive system are among the proposed possible effects of oxygen–ozone in management of musculoskeletal disorders [16, 17]. Since inaccurate injection can cause discomfort and significantly reduce the therapeutic effect, it is important that the injection is performed under imaging guidance [18]. In this study, we aimed to compare the therapeutic effects of intra-articular corticosteroid injection with oxygen–ozone injection in the treatment of knee osteoarthritis. All the injections of our study were performed under ultrasound guidance.

Material and methods

Study design and setting

This randomized clinical trial study was performed on 40–75-year-old patients with knee osteoarthritis who were referred to physical medicine and rehabilitation clinics of Iran University of Medical Sciences (Rasoul Akram and Firoozgar hospitals) between November 2016 and July 2017. The study was approved by ethics committee of Iran University of Medical Sciences, and the informed consent was obtained from all participants. This study is registered in clinical trial registry under number IRCT2016112724572N3.

Participants

The history, physical examination, and demographic information were taken for all patients by a physical medicine and rehabilitation specialist blinded to different groups of the study. Sixty-two patients with knee OA who met the inclusion criteria were enrolled and randomly assigned into two treatment groups; group A received steroid injection and group B underwent oxygen–ozone injection.

Inclusion criteria included the following: (1) knee OA based on the American College of Rheumatology criteria; (2) grades I, II (mild), and III (moderate) consistent with the Kallgren-Lawrence radiologic criteria; (3) knee pain for at least the last 6 months; and (4) 40–75 years of age.

Exclusion criteria included the following: (1) daily consumption of any type of sedatives, opioids, or non-opioid drugs for pain management by the patient throughout the study or during the follow-up period; (2) emergence of a pathology or trauma to the knee during the study and during the follow-up period; (3) existence of any infection; (4) pregnancy; (5) history of intra-articular knee injections during the last 3 months; (6) presence of certain inflammatory systemic diseases, such as lupus or rheumatoid arthritis or secondary osteoarthritis; (7) history of knee operations; (8) history of malignancy; (9) severe underlying disease/condition like uncontrolled diabetes or consumption of anticoagulants; (10) presence of contraindications for of oxygen–ozone therapy like known insufficient G6PD, uncontrolled hyperthyroidism, or leukemia.

Randomization, patient's enrolment, and blinding

To have a power of 0.80 with an alpha of 0.05 and accounting for 10% drop out, a sample of 31 participants was calculated for each group. All eligible subjects with chronic knee pain underwent conventional anteroposterior and lateral knee X-ray examination. There was no misalignment in the X-rays. Participants who met the inclusion criteria were assigned into two groups using randomly generated treatment allocations within sealed opaque envelopes produced by a statistician who was not involved in the recruitment. This led to groups with equal sample sizes and balanced distribution of important covariates, including gender, age, and duration of pain. The physician evaluating the outcome measures, participants, and the person responsible for data analysis were blinded.

Outcome measures

Before injection, primary outcome measures, including the visual analog scale (VAS), were used for evaluation of pain severity, and the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index was applied for assessment of symptom, functional limitations, stiffness, pain, and daily activities of all participants. In addition, clinical evaluations, including knee flexion range of motion (ROM) and the inspection for knee joint effusion, were performed. Knee effusion was measured in the suprapatellar recess using an ultrasound device in both groups. These indices were evaluated again at one week, one month, and three months after

intervention, and the results were compared before and after treatment for every group and between the two groups.

Pain intensity was measured using a 100 mm VAS and is referred as 0 to 100, where 0 meant no pain at all and 100 meant the worst pain possible. Patients were asked to mark a number on the VAS that corresponded to their average pain level at rest over the last 24 h.

The WOMAC is a 24-item questionnaire. It includes 5 items related to pain, 2 items related to stiffness, and 17 items related to physical function. Answers to each of the 24 questions are scored on 5-point Likert scales (none = 0, slight = 1, moderate = 2, severe = 3, extreme = 4), with total scores ranging from 0 to 96. Higher scores indicate greater disease severity. The WOMAC yields reliable scores that are highly sensitive to changes in pain and function in persons with OA of the knee [19, 20].

Active flexion knee ROM was measured using a goniometer with the patients in the prone position, hip in neutral. The goniometer axis was placed on the lateral aspect of the knee joint. Ultrasound examination was performed to evaluate joint effusion by scanning the area over the supra-patellar recess. Hitachi ARIETTA V60 (Hitachi Aloka Medical Systems, Tokyo, Japan) ultrasound device with a 5–18 MHz linear transducer was used. The patients were placed in the supine position with their knee flexed 20° resting on a rolled towel. First, the transducer was placed longitudinally on the patella, and then, the transducer was moved proximally toward the quadriceps tendon and muscle. The suprapatellar recess was then visualized between pre-femoral fat-pad in posterior and quadriceps tendon and suprapatellar fat-pad in anterior edge as a hypoechoic or anechoic fluid-containing area using high-frequency ultrasound. The suprapatellar recess was typically observed as a hypoechoic structure with a hyperechoic rim of synovial layer (Fig. 1). The largest anteroposterior diameter of the suprapatellar recess was measured at this level (Fig. 2).

All ultrasound examinations were performed by one expert with eight years of experience in musculoskeletal ultrasonography. During ultrasound examination, minimum amount of pressure was applied to skin to avoid compression and deformation of the suprapatellar recess, and the average of three measurements was recorded.

Intervention

Under sterile conditions and after prepping the skin with antiseptic while ultrasound probe was covered with a sterile barrier and using a sterile gel, the transducer was positioned longitudinally at the proximal edge of the patella. After visualizing the suprapatellar recess, the transducer was rotated 90° and positioned transversely along the distal portion of quadriceps tendon at the attachment point to the patellar bone. A total of 1 cc

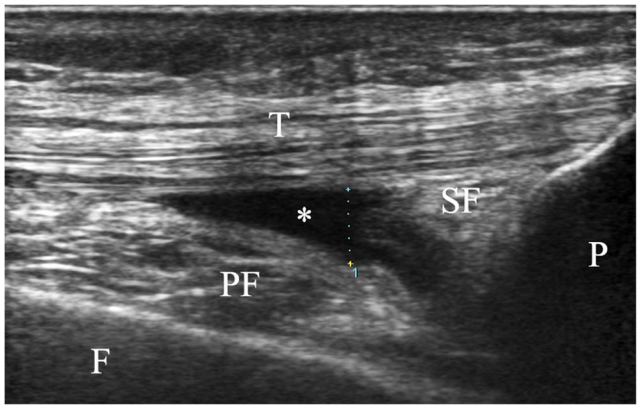

Fig. 1 Ultrasound image, longitudinal view of the suprapatellar pouch observed as a hypoechoic structure and measuring the maximum anteroposterior diameter (P, patella; F, femur; T, quadriceps tendons; SF, suprapatellar fat-pad; PF, prefemoral fat-pad; asterisks, suprapatellar pouch)

of lidocaine 2% was applied for local anesthesia of dermal and subdermal tissues in both groups. A 22-gauge 50-mm needle was then inserted from the lateral side of the knee at the level of the probe. Under real-time ultrasound guidance and using in-plane technique, the needle was passed from the lateral to the medial direction toward the suprapatellar recess (Fig. 3). After penetrating the synovial layer, the covered syringe was changed, and for group A, 40 mg triamcinolone (1 cc) and for group B, 10 cc of oxygen–ozone 15 microgram/milliliter (μg/ml) was injected under ultrasound guidance. All injections were performed by the same physiatrist with eight years of experience in musculoskeletal ultrasonography and ultrasound-guided interventions.

All patients were instructed to perform quadriceps muscle strengthening exercises before the injection. All of the participants were given written instructions to do each strengthening exercise (quad set and knee extension in sitting position) in ten repetitions three times a day throughout the course of the study. After injection, the patients were recommended to

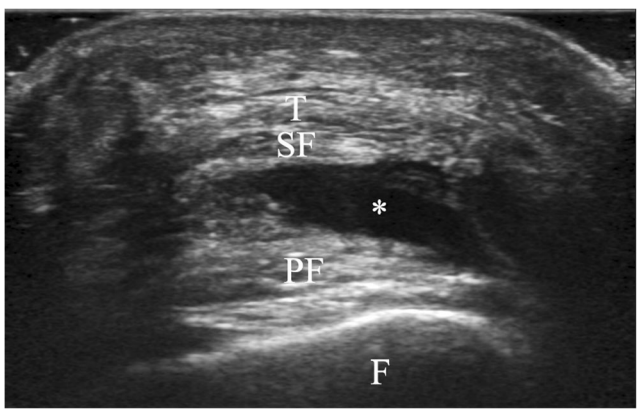

Fig. 2 Ultrasound image, transverse view of the suprapatellar pouch (F, femur; T, quadriceps tendons; SF, suprapatellar fat-pad; PF, prefemoral fat-pad; asterisks, suprapatellar pouch)

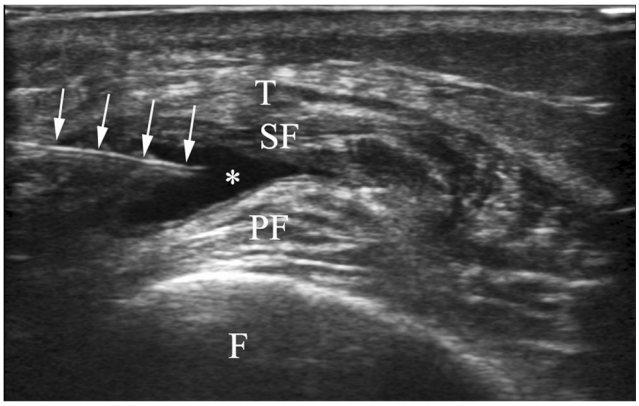

Fig. 3 Ultrasound-guided suprapatellar pouch injection in transverse (short axis) view (F, femur; T, quadriceps tendons; SF, suprapatellar fat-pad; PF, prefemoral fat-pad; asterisks, suprapatellar pouch; white arrows, needle)

apply cold pack on the needle insertion site for 5–10 min and could be repeated for 3–4 times a day.

Statistical analysis

Statistical analysis was performed by SPSS software V22, SPSS Inc., Chicago, IL, USA. Kolmogorov–Smirnov test showed normal data distribution. *t* test was used to compare the parametric data at baseline. Cross tabs and chi-square test were used to explore and compare the distribution frequency of sex and the side of involvement in each group. The interaction effects of time and group on outcomes were analyzed by mixed ANOVA and post-hoc complementary tests (CI = 95%). The significance level was considered to be less than 0.05.

Results

Sixty-eight patients with knee pain and diagnosis of knee osteoarthritis were assessed for eligibility. Five patients did not meet the criteria to enter the study, and one patient declined to participate in the study. Patients were randomly assigned into two groups: Thirty-one patients (3 male and 28 female) received steroid injection (group A) and 31 patients (7 male and 24 female) received oxygen–ozone treatment (group B). All 62 patients completed the three-month follow-up period (Fig. 4—flow diagram).

The patients included 52 (83.9%) females and 10 (16.1%) males. The mean age was 57.9 ± 9.2 years. The baseline demographic and clinical characteristics of the patients are presented in Tables 1 and 2. There was no significant difference in age, gender, and body mass index (BMI), the painful side, and the severity of knee involvement in X-ray between the two groups. No statistically significant difference was observed in the baseline values of study outcomes.

VAS

Data analysis showed that the mean score of VAS before the treatment period was 80.90 in group A and 77.35 in group B, which was not significantly different. A week after the injection, the score was 48.55 and 55.03, respectively. A month later, it was 48.52 and 53.97, respectively. Three months later, it was 62.65 and 53.16, respectively. Both treatment groups had a significant improvement in pain associated with their knee OA.

The interaction effects between time and group were statistically significant on VAS ($P = 0.41$). The groups showed different meaningful results in various time periods. The interaction effect of time and group with VAS in one week compared to three months after injection was significant ($P = 0.032$). It was also significant when VAS at one month was compared to three months after injection ($P = 0.015$). Both above-mentioned values were in favor of oxygen–ozone-taking group. The results of the interventions are detailed in Table 3 and Fig. 5.

Intra-group variations

In both steroid- and oxygen–ozone-taking groups, significant improvement was observed in various intervals with respect to the VAS score. According to Table 4, the VAS score of steroid-taking group was significant in the intervals: before injection—one week ($P < 0.001$), before injection—one month ($P < 0.001$), and before injection—three month ($P = 0.001$). Similarly, in the oxygen–ozone-taking group, the VAS score was significant in the following intervals: before injection—one week ($P < 0.001$), before injection—one month ($P < 0.001$), and before injection—three months ($P < 0.001$).

WOMAC questionnaire

Data analysis in Table 3 showed that the average WOMAC score for the patients before treatment was 67.87 for group A and 62.61 for group B, without any significant difference between the groups. The WOMAC score was 52.32 and 58.29, respectively, a week after injection, 43.23 and 52.65 one month after injection, and 51.61 and 47.81 three months after injection.

The interaction effects of group and time were significant on the outcome ($P = 0.019$), and the amount of improvement was statistically different between the two groups.

As shown in Table 3, the interaction effects of group and time on the outcome was significant in intervals 1 to 2 (before injection—one week after injection) with *P* value = 0.021 and 1 to 3 (before injection—one month after injection) with *P* value = 0.010, in favor of the steroid-taking group. Also, the WOMAC score in the oxygen–ozone-taking group was

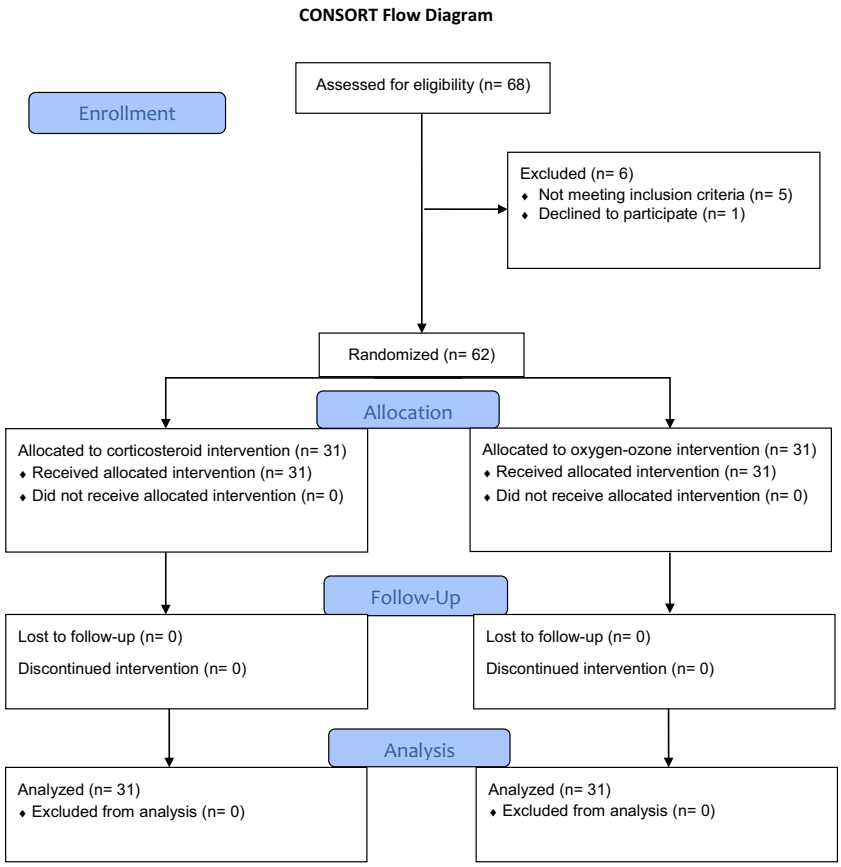

Fig. 4 Flow chart of included and excluded participants

significant compared to the steroid-taking group in the intervals of 1–3 months ($P = 0.003$). In the same interval, the average WOMAC score was increased (worsened) in the steroid taking, as compared to oxygen–ozone-taking, group (Table 2 and Fig. 5).

Intra-group variations

Significant differences were observed in both groups between various time intervals (Table 4). In both groups, the WOMAC score was significantly changed in the study time intervals. The WOMAC score in the steroid group was significant in the following time intervals: before injection—one week ($P < 0.001$), before injection—one month ($P < 0.001$), and before injection—three months later ($P < 0.001$). In the steroid group, the WOMAC score was also significant in the time interval between one month and three months ($P = 0.039$(.

In the oxygen–ozone group, the WOMAC score was only significant in the time interval between before injection and three months after the injection ($P = 0.002$).

Table 1 Comparison of demographic indices between corticosteroids and oxygen–ozone groups

Group	Drugs	Number	Mean	SD	*P* value
Age	Corticosteroids	31	56.26	7.887	0.090
	Ozone	31	59.65	10.249	
BMI	Corticosteroids	31	29.22	4.53	0.771
	Ozone	31	28.83	2.46	
Pain duration	Corticosteroids	31	5.58	1.544	0.807
	Ozone	31	5.61	1.308	

ROM (range of motion)

Data analysis in Table 3 showed that the average ROM score in patients before the treatment period was 111.55° in group A and 106.84° in group B, which was not significantly different. The mean knee ROM was 112.06 vs 109.19° one week after injection, 112.61 vs 109.10° one month after injection, and 109.92 vs 110.26° three months after injection, respectively. None of which were statistically significant ($P = 0.880$) considering interaction effect between time and group (Table 2 and Fig. 5).

Inter-group variations

According to Table 4, there was no significant knee ROM change in the two groups in different intervals.

Table 2 Comparison of demographic indices between corticosteroids and oxygen–ozone groups

Variable	Group	Type of drugs		Total	*P* value
		Corticosteroids	Ozone		
Sex	Male	3	7	10	0.301
	Female	28	24	52	
Frequency of right or left knee	Right	17	15	32	0.258
	Left	14	16	30	
Grading of knee OA	Grade 1	3	0	3	0.258
	Grade 2	12	15	27	
	Grade 3	16	16	32	

Articular effusion in ultrasound examination

Data analysis in Table 3 showed that before the injection the average articular effusion was 4.0761 cm in group A and 4.8065 cm in group B, which was not significantly different. This value was 3.2294 vs 3.7558 cm one week after injection, 3.1471 vs 3.6368 cm one month after injection, and 3.1718 vs 3.0345 cm three months after injection.

The interaction effects of group and time on this outcome measure were not significant ($P = 0.362$); and the variations in the time intervals are not statistically different between the two groups (Table 2 and Fig. 5).

Intra-group variations

As observed in Table 4, the articular effusion index change in the steroid group was not statistically significant in any of the time intervals; however, in the oxygen–ozone group, the articular effusion was significantly improved between the time interval before injection and one week after injection ($P = 0.044$). It was also significant between the interval before injection and three months after the injection ($P < 0.001$).

Safety

There were no reported complications after the injection of corticosteroids or oxygen–ozone in both groups throughout the length of study.

Discussion

In this study, 62 patients with knee osteoarthritis were randomly assigned into two groups to receive steroid or oxygen–ozone injection. The study intended to compare four different outcome measures among patients receiving ultrasound-guided injection of steroid vs oxygen–ozone for the treatment of knee osteoarthritis in intervals up to 3 months follow-up.

Our data revealed that the interaction effects of group and time were significant on pain severity evaluated by VAS in the beginning of the study (before injection), and one week, one month, and three months after the injection. This study showed that the positive effects of the steroid injection in VAS was significant one week after the injection and sustained for one month. Although in comparison to the baseline the patients who received steroid injection had lower VAS score 3 months after the injection, their VAS at this point showed a significant increase ($P = 0.008$) (worsening of pain) when compared to their VAS score in one month after the injection (Fig. 5).

The WOMAC index was also improved significantly in both groups. Similar to what we saw in VAS comparison, the WOMAC score improved more significantly one week and one month after the injection in patients who received steroid injection. However, despite of continuous positive benefit in patients who received oxygen–ozone injection, three months after the baseline, the WOMAC index increased among the patients who received steroid (Fig. 5).

The interaction effects of group and time was not significant on two other outcome measures (flexion ROM and effusion in suprapatellar recess) among patients who received steroid injection. However, there was statistically significant decrease in amount of ultrasound findings of effusion among patients who received oxygen–ozone during the time intervals between baseline and one week after the injection and between baseline and three months after the injection.

There are different treatment options for knee OA, such as exercise (especially aquatic), oral and topical NSAIDs, acetaminophen, intra-articular corticosteroid injections, and tramadol. There is no recommendation regarding the use of intra-articular hyaluronates, and recommendations are against the use of chondroitin sulfate, glucosamine, and topical capsaicin [21].

In a study by Hashemi et al., they showed that oxygen–ozone is effective in reducing pain among patients with knee osteoarthritis [22]. This is consistent with the findings of our study. Hashemi et al. included mild to moderate knee OA patients, such as in our study. They injected oxygen–ozone for one group and dextrose (prolotherapy) for the other group. Intervention repeated for three times with 10-day intervals, and outcome measures were only VAS and WOMA which

Table 3 The results of the oxygen–ozone and corticosteroid intervention on the intensity of VAS, ROM (range of motion), WOMAC questionnaire, and joint effusion

Variable	Time of intervention	Type of drugs	Mean	SD		*P* value		*P* value
VAS	First visit	Corticosteroids	80.90	14.750	Group and time interaction	0.041	First visit vs. 3 months	0.355
		Ozone	77.35	16.382				
		Total	79.13	15.562			1 week vs. 3 months	0.032
	After 1 week	Corticosteroids	48.55	25.270				
		Ozone	55.03	22.222			1 month vs. 3 months	0.015
		Total	51.79	23.825				
	After 1 month	Corticosteroids	48.52	28.452			First visit vs. 1 month	0.086
		Ozone	53.97	25.234				
		Total	51.24	26.811			1 week vs. 1 month	0.877
	After 3 months	Corticosteroids	62.65	31.166				
		Ozone	53.16	26.771				
		Total	57.90	29.206				
ROM (range of motion)	First visit	Corticosteroids	111.55	12.630	Group and time interaction	0.880	First visit vs. 3 months	0.145
		Ozone	106.84	12.691				
		Total	109.19	12.779				
	After 1 week	Corticosteroids	112.06	11.480				
		Ozone	109.19	12.136			1 week vs. 3 months	0.419
		Total	110.63	11.805				
	After 1 month	Corticosteroids	112.61	13.086				
		Ozone	109.10	10.744				
		Total	110.85	12.005			1 month vs. 3 months	0.248
	After 3 months	Corticosteroids	110.26	13.256				
		Ozone	109.58	10.194				
		Total	109.92	11.732				
WOMAC questionnaire	First visit	Corticosteroids	67.87	20.709	Group and time interaction	0.019	First visit vs.1 week	0.021
		Ozone	62.61	20.871				
		Total	65.24	20.788			First visit vs. 1 month	0.010
	After 1 week	Corticosteroids	52.32	27.020			First visit vs. 3 months	0.792
		Ozone	58.29	22.899				
		Total	55.31	25.020				
	After 1 month	Corticosteroids	43.23	22.390			1 week vs. 1 month	0.552
		Ozone	52.65	20.684				
		Total	47.94	21.898				
	After 3 months	Corticosteroids	51.61	26.370			1 month vs. 3 months	0.003
		Ozone	47.81	20.186				
		Total	49.71	23.368				
Joint effusion	First visit	Corticosteroids	4.0761	2.025	Group and time interaction	0.369	First visit vs.1 week	0.705
		Ozone	4.8065	2.768				

Table 3 (continued)

Variable	Time of intervention	Type of drugs	Mean	SD	*P* value		*P* value
		Total	4.4413	2.433			
	After 1 week	Corticosteroids	3.4926	1.739			
		Ozone	3.1471	1.533		First visit vs. 3 months	0.140
		Total	3.6368	2.134			
	After 1 month	Corticosteroids	3.3919	1.859			
		Ozone	3.1718	1.631		1 week vs. 1 month	0.940
		Total	3.0345	1.288			
	After 3 months	Corticosteroids	3.1032	1.459			
		Ozone	4.0761	2.025		1 month vs. 3 months	0.126
		Total	4.8065	2.768			

were evaluated before the first injection and three months later. In comparison to the present study, we performed single injection for each participant and we also measured ROM and joint effusion alongside subjective outcome measures (VAS, WOMA), before injection, 1 week, 1 month, and 3 months after treatment. Their injections were done blindly; however, our injections were performed under ultrasound guidance.

Giombini et al., in a study in 2016, compared the effects of the intra-articular injection of hyaluronic acid, oxygen–ozone, and the combination of both in treatment of knee osteoarthritis. They showed that all three groups including oxygen–ozone injection improve Knee Injury and Osteoarthritis Outcome Scores (KOOS) up to two months after the treatment [23]. They performed injections one per week for 5 weeks. Outcome measures were only KOOS and VAS, evaluated before treatment, at the fifth injection, and at 2 months after treatment. This is comparable with our findings. In comparison to the present study, we evaluated single injection of oxygen–ozone and corticosteroid with four outcome measures and 3-month follow-up. Another study by Duymus et al. [-24]compared the platelet-rich plasma with hyaluronic acid and ozone therapy. They showed that all three options are effective in management of the symptoms of mild to moderate knee OA. However, the positive outcome after platelet-rich plasma injection was shown to be superior to hyaluronic acid, and hyaluronic acid was showed better outcome than ozone injection with respect to VAS and WOMAC. In their study, these indices got worse on the third month for all three groups dominantly in the ozone group compared to platelet-rich plasma (PRP) and hyaluronic acid. This could be due to higher doses in their study (four doses of 15 ml of 30 μg/ml oxygen–ozone). This issue highlights the necessity for finding best possible dose of oxygen–ozone in knee OA. Although they did not compare ozone to corticosteroid, their findings are in contrast to our results on continued improvement of VAS and WOMAC at three months after oxygen–ozone injection. Furthermore, in our study, the patients were not allowed to take analgesics during the course of the study. In their study, there was no limitation in use of analgesics.

Raeissadat et al. [25] compared hyaluronic acid and oxygen–ozone in knee OA. They performed three weekly injections with outcome measures including only VAS and WOMAC. Results showed that both hyaluronic acid and oxygen–ozone can be effectively used in knee OA patients and neither of the two had any superiority. Findings about the effectiveness of oxygen–ozone were similar to our findings.

Al-Jaziri and Mahmoodi showed similar results to our study in terms of long-term effects of oxygen–ozone injection. They focused on painkilling effects of oxygen–ozone injection on spine and knee osteoarthritis [13]. Giurazza et al. [26] focused their study on the effects of intradiscal injection of oxygen–ozone on backache. They also reported positive long-

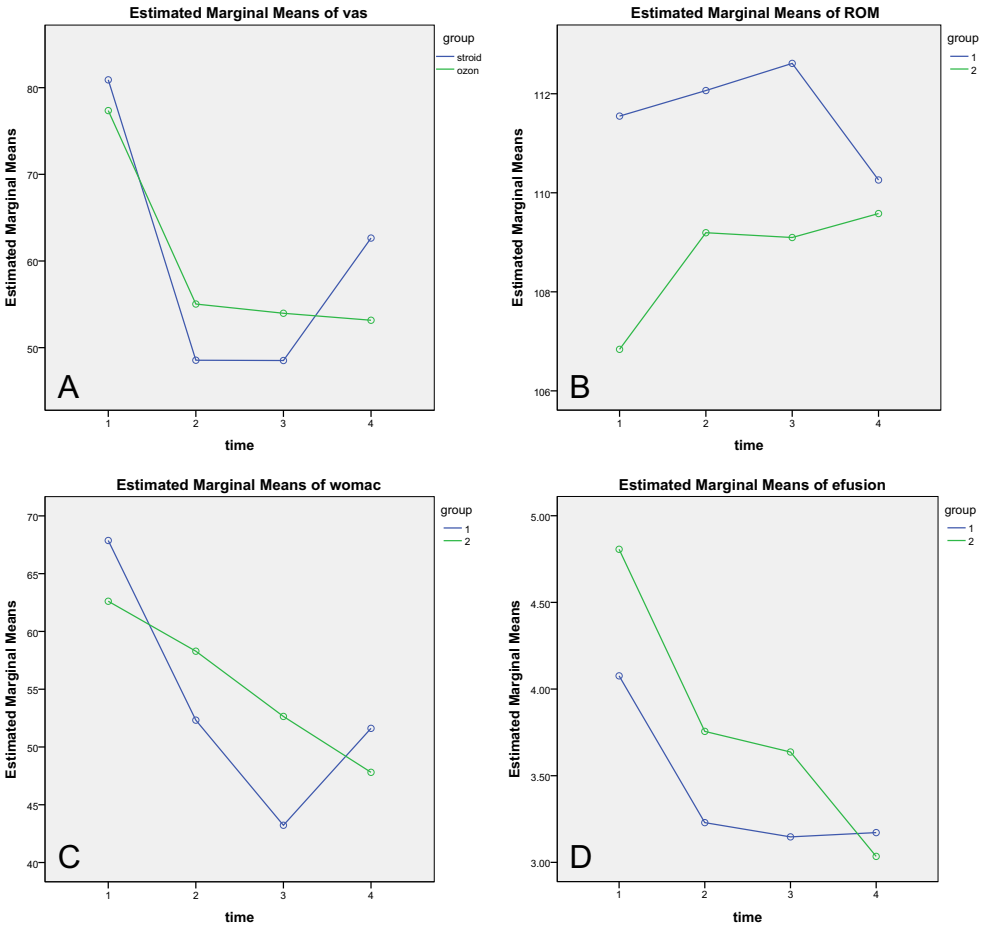

Fig. 5 Intra-group analysis of the VAS (**a**), ROM (**b**), WOMAC questionnaire (**c**) and joint effusion (**d**) in two groups of ozone and corticosterone recipient

term effects of the oxygen–ozone in relieving pain. Intra-articular steroid injection provided similar short-term pain relief and improvement of KOOS and/or WOMAC in our study vs others [27, 28]. Faúndez et al. [29] also showed the effects of steroid on short-term pain relief and its ineffectiveness in long term for patients with knee OA. The results by Fatimah et al. [30] also were similar to ours in terms of VAS and WOMAC indices after intra-articular steroid injection. A study by Lemont et al. showed that both triamcinolone hexacetonide and methylprednisolone acetate injection are equally effective on pain relief and functional improvement in knee OA [31].

Table 4 Intra-group analysis of the VAS, ROM, WOMAC questionnaire, and joint effusion in two groups of oxygen–ozone and corticosterone recipients

Variables	Type of drugs	Time of intervention	VAS	ROM (range of motion)	WOMAC questionnaire	Joint effusion
Intragroup changes	Corticosteroids	First visit vs. 1 week	< 0.001	1.000	< 0.001	0.175
		First visit vs. 1 month	< 0.001	1.000	< 0.001	0.230
		First visit vs. 3 months	0.001	1.000	0.001	0.189
		1 week vs. 1 month	1.000	1.000	0.176	1.000
		1 week vs. 3 months	0.049	1.000	1.000	1.000
		1 month vs. 3 months	0.008	1.000	0.039	1.000
	Oxygen–ozone	First visit vs. 1 week	< 0.001	0.682	1.000	0.044
		First visit vs. 1 month	< 0.001	1.000	0.077	0.059
		First visit vs. 3 months	< 0.001	0.962	0.002	< 0.001
		1 week vs. 1 month	1.000	1.000	1.000	1.000
		1 week vs. 3 months	1.000	1.000	0.100	0.137
		1 month vs. 3 months	1.000	1.000	0.651	0.236

Although in this study the articular effusion in the oxygen–ozone group was significantly improved between the time interval before injection and one week after injection, the interaction effects of group and time on ROM and articular effusion in ultrasound examination were not significant. These findings indicate that knee flexion ROM and articular effusion in ultrasound examination are not responsive to this intervention and are not showing significant improvement in three months follow-up. This finding could be due to short follow-up period or the nature of degenerative joint changes in knee OA.

We did not find any published article comparing intra-articular ozone injection with corticosteroid injection in patients with knee osteoarthritis.

The present study is probably the first report evaluating these two treatments, and therefore, we cannot compare our findings with previous ones. However, the findings of this study must be interpreted in view of its limitations. The main limitation was the relatively small sample size and limited follow-up period (three months). Another limitation was the fact that we were not able to blind the injecting physician due to the nature of the interventions. Finally, we did not include a control group (receiving no injection) in this study, and therefore, we cannot compare the results with placebo. This study was the first on this topic, and further studies, with larger sample size and longer follow-up which also include more ultrasound diagnostic parameters, are warranted to compare these methods.

Conclusions

Both steroid and oxygen–ozone injections are effective in management of patients with knee osteoarthritis. Although steroid injection shows an earlier improvement in symptoms of knee OA, the effects of oxygen–ozone injection seem to be persistent and last longer.

Acknowledgements The present study was supported by the Vice-chancellor for Research, IUMS (Iran University of Medical Sciences), Iran.

Compliance with ethical standards

Disclosures None.

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