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Comparison of the Efficacy of Dextrose Prolotherapy and Ozone in Patients with Knee Osteoarthritis: A Randomized Cross-Sectional Study

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Abstract: This study aimed to compare the effectiveness of dextrose prolotherapy, ozone therapy, and home exercise programs in patients with knee osteoarthritis. Seventy-five patients with knee osteoarthritis were divided into three groups, with 25 in each group. At week 0 (baseline), week 3, and week 6, 12.5% dextrose (intraarticular and periarticular) was administered to the dextrose prolotherapy group. At week 0 (baseline), week 1, and week 2 15 µg/mL ozone (intraarticular and periarticular) was administered to the ozone therapy group. Both groups were also given a home exercise program. The third group was given a home-based exercise therapy program for 12 weeks. All groups were evaluated for VAS, WOMAC, TUG, ROM-active, and ROM-passive values at weeks 0 (baseline), 6, and 12. Ozone therapy more effectively improved VAS scores than dextrose prolotherapy and VAS and WOMAC scores than home-based exercise therapy in the 6th week. Ozone therapy also more effectively improved VAS and WOMAC-stiffness scores than dextrose prolotherapy and VAS, WOMAC, and ROM-active scores than home-based exercise therapy in the 12th week. Both dextrose prolotherapy and ozone therapy are effective in knee osteoarthritis treatment. Ozone therapy should be used in suitable cases rather than dextrose prolotherapy.

Keywords: dextrose prolotherapy; exercise; knee; osteoarthritis; ozone therapy

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1. Introduction

Osteoarthritis, a degenerative joint disease, is an important cause of pain and disability in all societies [1]. Exercise therapies that strengthen the knee muscle are effective in reducing pain [2]. Myofascial trigger points are related to pain sensation and joint function [3]. Research and clinical applications related to regenerative therapies including targeting of these points in the treatment of knee osteoarthritis (KOA) are increasing [4]. These treatments aim to heal the tissues that cannot be repaired using the body's repair mechanisms. These regenerative treatments include the use of platelet-rich plasma (PRP) [4], mesenchymal stem cells [5], hyaluronic acid (HA) [6,7], dextrose prolotherapy (DPT) [4,8], and ozone therapy (OT) [9]. The use of intraarticular injections in the treatment of knee OA is common, but their effectiveness is controversial [10,11].

DPT is a regenerative injection technique lasting several sessions. Small amounts of a solution are introduced into painful and degenerated tendon insertions (enthesis), joints, ligaments, and adjacent joint spaces to promote the growth of normal cells and tissues [8,12]. The most common prolotherapy agent used in clinical practice is dextrose, with concentrations ranging from 12.5% to 25% [13]. However, the mechanism of action of DPT has not been fully elucidated [8]. It is thought to affect the healing process through tissue proliferation and remodeling by initiating local inflammation [14] and stimulating

growth factors [15]. DPT application in the treatment of KOA provides positive benefits in functional gains [16–18]. PT is conditionally recommended for the treatment of KOA in the 2019 American College of Rheumatology (ACR) guidelines for the treatment of KOA [19].

The use of ozone therapy (OT), another treatment method, in the outpatient treatment of KOA is increasing [20]. Ozone therapy has the advantages of being safe to use in intraarticular (IA) approaches and ease of application [21]. Ozone has analgesic, anti-inflammatory effects via stimulation of antioxidant mechanisms, vasodilatation, and angiogenesis [20,22]. OT provides significant improvement in pain and function in the short and medium term treatment of KOA [23,24]. The sources of pain in KOA are the joint capsule, ligaments, synovium, bone, lateral part of the meniscus, tendons and extra-articular ligaments [23,24]. The standard "whole joint" injection method includes IA injections (IA) and multiple periarticular (PA) injections into soft tissues [25]. The whole joint injection method may more effectively reduce pain and improve functional status due to its effects on many points that are the source of pain. There are studies in which DPT has been applied together as IA and PA injections in KOA [26–28]. On the other hand, there is no study in which OT is applied using both IA and PA injections, like DPT. The current study applied DPT and ozone treatments to KOA patients with IA and PA methods. The pain relief and improvement in joint function of these treatments were compared with each other and with the home-based exercise treatment program.

2. Materials and Methods

2.1. Sample Size Calculation

The minimum number of patients required for the study was calculated in the G Power sample calculation program (version 3.1.9.4). Since the study protocols (such as the duration of treatment, determination of WOMAC values, and dextrose concentration) of studies conducted with similar purposes in the literature differ from the study we planned, the sample size was calculated by taking the effect size (Cohen's f) of 0.4 for the repeated samples (ANOVA) consisting of 3 groups at the level of Type I error (α) 0.05 and Type II error (1-β) 0.95. Accordingly, the minimum sample size was calculated as 24 for each group. However, considering that the study duration was 12 months and that there may have been people who could not complete the study, 25 people were initially assigned to each group. Volunteers between the ages of 40–70 were included in each group (75 volunteers in total).

2.2. Patient Selection

This prospective, randomized, cross-sectional, control group study included 75 volunteer male and female patients diagnosed with primary knee osteoarthritis (KOA) and aged between 40–70 years. Patients were randomly divided into 3 groups (prolotherapy, ozone therapy, and exercise groups), each with 25 patients.

Inclusion criteria were: being diagnosed with primary KOA according to ACR clinical/radiological diagnostic criteria, not responding to conservative treatments for at least 3 months, having a score of 2 or 3 from the Kellgren–Lawrence radiologic scoring system (scores ranging from 0 to 4 grades), and age of between 40–70 years.

Exclusion criteria were: history of trauma, surgery, or any invasive procedure on the affected joint in the past 6 months; secondary osteoarthritis due to systemic diseases; uncontrolled diabetes mellitus; rheumatological diseases; systemic infection; tuberculosis; malignancy; hyperthyroidism; severe cardiovascular disease; glucose-6-phosphate dehydrogenase deficiency; abnormalities in hemogram and coagulation tests; total knee replacement, undergoing anti-inflammatory, anticoagulant, or immunosuppressive therapy; taking a nonsteroidal anti-inflammatory drug (NSAID) in the last week; taking steroid drugs in the last month; using angiotensin converting enzyme inhibitors; knee injection in the last 6 months; and pregnancy and breastfeeding.

2.3. Ethical Issues

The study was approved by the Clinical Research Ethics Committee of Ataturk University Faculty of Medicine (26 June 2020/373). The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000. An informed consent form was obtained from all participants, who were informed of all matters related to the study.

2.4. Study Design

Study design and applied therapies are summarized in Figure 1.

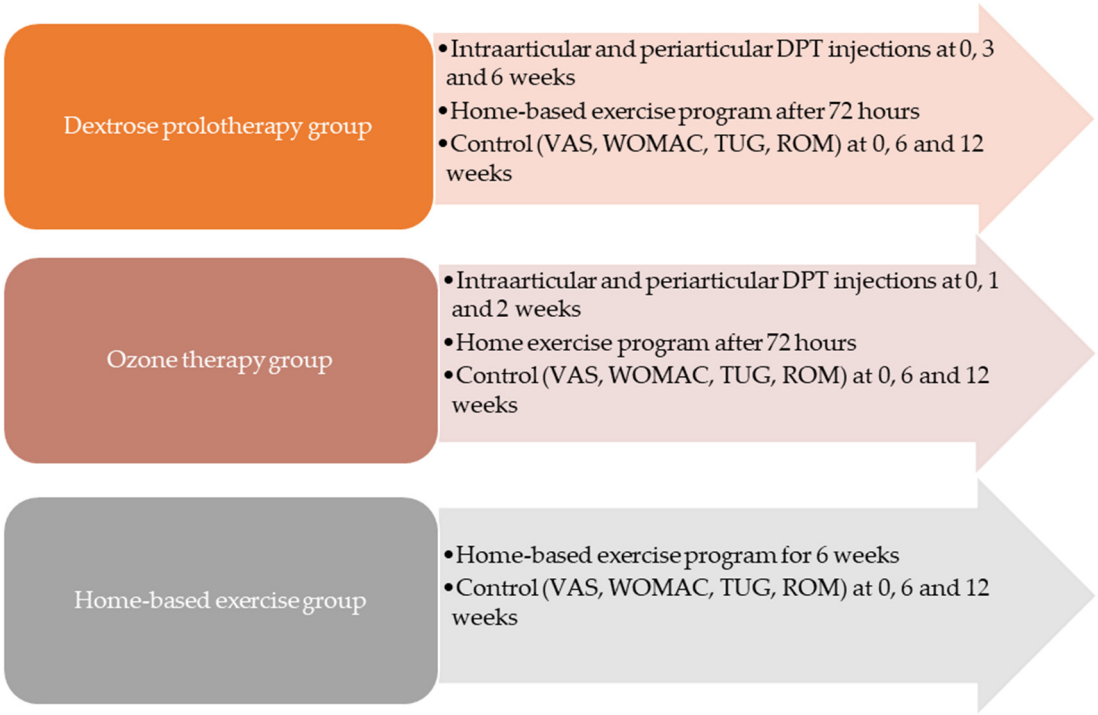

Figure 1. Study design.

2.4.1. Dextrose Prolotherapy Group

The procedure was performed by a qualified physical medicine and rehabilitation doctor. Dextrose solution concentration was set to 12.5% by using 5% and 20% dextrose concentrations in equal volumes. According to the VAS score, the patient was asked to define the pain in both knees, and DPT was applied to the more painful knee on the 0th, 3rd, and 6th weeks. Intraarticular 5 mL 12.5% dextrose was applied with a lateral approach. Periarticular 1 mL 12.5% dextrose was applied to 10 points with a total volume of 10 mL. The points were medial and lateral coronary ligaments, proximal and distal medial and lateral collateral ligaments, the quadriceps tendon region of patella upper edge, the distal and proximal region of the patellar tendon, and the tendon region of pes anserine (Figure 2).

2.4.2. Ozone Therapy Group

A qualified anesthesia and reanimation doctor performed the procedure. Ozone therapy was performed using both intraarticular and periarticular methods. According to the VAS score, the patient was asked to define the pain in both knees, and ozone therapy was applied to the more painful knee on the 0th, 1st, and 2nd weeks. The patient was in a sitting position, and the knee was flexed. Lidocaine was injected (2%, 2 mL) to reduce pain before ozone therapy. Intraarticular 15 mL ozone solution (15 μg/mL) was applied with a lateral approach once a week for three weeks (0th, 1st, and 2nd). Periarticular 1 mL ozone solution was applied to 10 points with a total volume of 10 mL. The points were medial

and lateral coronary ligaments, proximal and distal medial and lateral collateral ligaments, the quadriceps tendon region of patella upper edge, the distal and proximal region of the patellar tendon, and the tendon region of pes anserine (Figure 2).

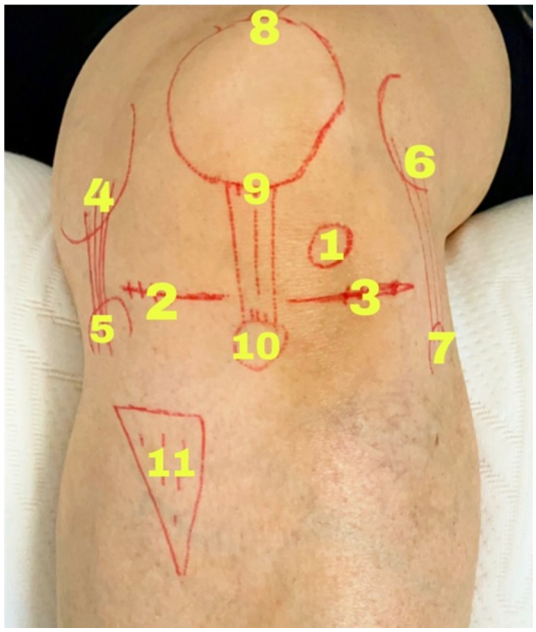

Figure 2. Periarticular injection sites of DPT and OT in the knee with osteoarthritis. (1: intraarticular injection site, periarticular injection sites: 2: medial region of coronary ligament, 3: lateral region of coronary ligament, 4: proximal region of medial collateral ligament and femur, 5: distal region of medial collateral ligament and tibia, 6: proximal region of lateral collateral ligament and femur, 7: distal region of lateral collateral ligament and head of the fibula, 8: quadriceps tendon region of patella, 9: proximal region of the patellar tendon, 10: distal region of the patellar tendon and tuberositas tibia, 11: tendon region of pes anserine).

2.4.3. Home-Based Exercise Group

All patients performed the routinely applied home-based exercise program of our clinic. This program consisted of isometric and isotonic exercises to strengthen quadriceps muscle and improve range of motion (ROM). Exercises were performed with 2 sessions/day, 10 times/session for 12 weeks. Exercises were explained with practice and written documents with images were provided to use by the patients. The protocol consisted of 7 movements; each movement was performed first on the right knee, and after a few seconds of relaxation, on the left knee (10 times counting to 10). Only the second movement was performed on both knees at the same time. Exercise protocol details of the afore-mentioned 7 exercises are explained as follows:

i. Sitting on a chair, stretch your legs and place a rolled towel under your right knee. Straighten your leg by stretching your knee, pressing your knee down.
ii. Sitting on a chair, stretch your legs and place a rolled towel between your knees, count to 10, then relax for a few seconds.
iii. In the supine position, with the knee straight, raise your right leg 15–30 cm, count to 10, then relax for a few seconds.
iv. In the supine position, straighten your legs, and pull your right leg towards you for a count of 10, then relax.
v. Lie face down and bend your right knee (pull it towards you), count to 10, then relax for a few seconds
vi. Lie on your side, bend your right leg and hip towards you, and count to 10. Then straighten your leg and extend your back as far as you can, then relax for a few seconds.

2.5. Outcome Assessment

Outcome measures were assessed at baseline (week 0), week 6, and week 12. A visual analog scale (VAS) was used to evaluate pain as follows: VAS at rest (VAS-rest) and VAS at movement (VAS-movement). The Western Ontario and Mc Master Universities Osteoarthritis Index (WOMAC) was used to evaluate functional status and disability as follows [29]: WOMAC-stiffness, WOMAC-function (physical function), and WOMAC-total (sum of WOMAC-pain, WOMAC-stiffness, and WOMAC-function). Range of motion (ROM) was determined with active (ROM-active) and passive (ROM-passive) goniometric measurements. The timed up-and-go test (TUG) was used to evaluate the fall risk.

2.6. Statistical Analysis

Statistical analyses were performed in SPSS version 23.0 (SPSS, Chicago, IL, USA) package program. Normality of data was determined with the Kolmogorov–Smirnov test. Descriptive statistics were presented as mean ± standard deviation values. p values of <0.05 at the 95% confidence interval were considered statistically significant. A one-way ANOVA test was used to compare values of HEP, DPT, and OT groups. Tukey's test was used to determine post hoc comparisons of the one-way ANOVA test (comparing values of exercise, prolotherapy and ozone groups and differences). The repeated measures one-way ANOVA test was used to compare the same group's baseline, 6th week, and 12th week values in the same group. The Bonferroni test was used to determine comparisons of the baseline, 6th week, and 12th week values. The eta-squared value (η2) was used to determine effect sizes. Eta-squared shows how much the independent variable or factor explains the total variance in the dependent variable and varies between 0.00 and 1.00. η2 values of 0.01, 0.06, and 0.14 were interpreted as "small", "medium", and "large" effect sizes, respectively.

3. Results

The demographic and clinical characteristics of all patients are summarized in Table 1.

Table 1. The demographical and clinical characteristics of the patients.

Characteristics and Clinical Features	Total Patients with KOA (n = 75)	Dextrose Prolotherapy (n = 25)	Ozone Therapy (n = 25)	Home-Based Exercise Therapy (n = 25)	*p*
Age (years)	56.7 ± 7.3	56.6 ± 7.1	57.0 ± 7.6	56.5 ± 7.4	0.967
Female sex—n (%)	64 (%85.3)	21 (%84)	22 (%88)	21 (%84)	0.899
Smoker—n (%)	6 (%8)	2 (%8)	1 (%4)	3 (%12)	0.600
BMI (kg/m^2)	33.10 ± 4.98	34.3 ± 4.6	33.2 ± 4.4	32.2 ± 5.4	0.245
Duration of clinical disease (months)	33.43 ± 29.47	35.1 ± 29.6	34.3 ± 27.6	30.8 ± 31.9	0.864
More symptomatic knee, n (%)					0.288
Right	51 (%68)	18 (%72)	17 (%68)	16 (%64)	
Left	24 (%32)	7 (%28)	8 (%32)	9 (%36)	
Grade of KOA, n (%)					0.958
Grade II	46 (%61.3)	16 (%64)	15 (%60)	15 (%60)	
Grade III	29 (%38.7)	9 (%36)	10 (%40)	10 (%40)	

There was no significant difference in terms of age, gender, BMI values, or clinical features of patients ($p > 0.05$ for all comparisons). All outcome parameters (VAS, WOMAC, TUG, and ROM) were evaluated at 0, 6, and 12 weeks. VAS-rest and VAS-movement results of all groups and comparisons are given in Table 2.

Table 2. VAS scores of groups and comparisons.

VAS-Rest	Groups			*p*	η2
	Dextrose Prolotherapy (n = 25)	**Ozone Therapy (n = 25)**	**Home-Based Exercise Therapy (n = 25)**		
Baseline value	5.08 ± 2.06	9.71 ± 0.55	5.84 ± 2.70	<0.01 ** [a] 0.376 [b] <0.01 ** [c] <0.01 **	0.513
6th week	−1.44 ± 1.73	−7.08 ± 2.01	−0.56 ± 1.66	<0.01 ** [a] 0.216 [b] <0.01 ** [c] <0.01 **	0.217
12th week	−2.08 ± 2.04	−7.08 ± 2.01	−1.68 ± 1.70	0.045 * [a] 0.744 [b] <0.01 ** [c] <0.01 **	0.108
p	<0.01 **	<0.01 **	<0.01 **		
Baseline-6th week	[d] 0.01 **	[d] <0.01 **	[d] 0.314		
Baseline-12th week	[d] <0.01 **	[d] <0.01 **	[d] <0.01 **		
VAS-movement					
Baseline	7.92 ± 1.77	9.75 ± 0.53	8.20 ± 1.32	<0.01 ** [a] 0.733 [b] <0.01 ** [c] <0.01 **	0.276
6th week	−2.48 ± 1.71	−5.96 ± 1.96	−1.60 ± 1.97	<0.01 ** [a] 0.233 [b] <0.01 ** [c] <0.01 **	0.296
12th week	−4.00 ± 2.27	−5.88 ± 1.98	−2.12 ± 1.59	<0.01 ** [a] 0.003 ** [b] <0.01 ** [c] 0.003 **	0.288
p	<0.01 **	<0.01 **	<0.01 **		
Baseline-6th week	[d] 0.01 **	[d] 0.01 **	[d] 0.01 **		
Baseline-12th week	[d] <0.01 **	[d] <0.01 **	[d] <0.01 **		

Results are expressed as mean ± standard deviation. *p*: one-way ANOVA test statistics *p* value (comparison of different columns) and repeated measures one-way ANOVA test statistics *p* value (comparison of time effect in the same column). *: $p < 0.05$, **: $p < 0.01$. Superscript letters a,b,c express *p* values of Post hoc Tukey's test results of one-way ANOVA test (comparison of different columns); [a]: comparison of differences in dextrose prolotherapy and exercise groups, [b]: comparison of differences in exercise and ozone groups, [c]: comparison of differences in prolotherapy and ozone groups. Superscript letter [d] expresses the *p* value of Bonferroni test result of repeated measures one-way ANOVA test (comparison of mean baseline, 6th week, and 12th week values in the same group). η2: eta-squared value of one-way ANOVA test between different groups.

WOMAC-stiffness, WOMAC-function, and WOMAC-total results of all groups and comparisons of differences are given in Table 3.

Table 3. WOMAC scores of groups and comparisons.

WOMAC-Stiffness					
Baseline	4.20 ± 1.80	5.21 ± 1.81	4.72 ± 2.01	0.120	0.047
6th week	−1.52 ± 1.63	−2.96 ± 1.45	−0.40 ± 1.44	<0.01 ** [a] 0.029 * [b] <0.01 ** [c] 0.004 **	0.204
12th week	−1.80 ± 1.75	−2.96 ± 1.45	−1.12 ± 1.61	0.001 ** [a] 0.302 [b] <0.01 ** [c] 0.035 *	0.128
p	<0.01 **	<0.01 **	<0.003 **		
Baseline-6th week	[d] <0.01 **	[d] <0.01 **	[d] <0.536		
Baseline-12th week	[d] <0.01 **	[d] <0.01 **	[d] <0.006 **		
WOMAC-function					
Baseline	38.60 ± 11.81	39.50 ± 6.69	40.00 ± 15.33	0.898	0.003
6th week	−12.64 ± 11.79	−17.56 ± 5.03	−6.48 ± 9.88	<0.01 ** [a] 0.058 [b] <0.01 ** [c] 0.158	0.148
12th week	−18.64 ± 13.13	−17.56 ± 5.02	−10.04 ± 9.26	0.005 ** [a] 0.007 ** [b] 0.021 * [c] 0.919	0.158
p	<0.01 **	<0.01 **	<0.01 **		
Baseline-6th week	[d] <0.01 **	[d] <0.01 **	[d] 0.01 **		
Baseline-12th week	[d] <0.01 **	[d] <0.01 **	[d] <0.01 **		
WOMAC-total					
Baseline	55.90 ± 17.02	58.00 ± 9.48	57.64 ± 21.45	0.844	0.003
6th week	−18.93 ± 15.71	−26.80 ± 7.90	−8.86 ± 14.60	<0.01 ** [a] 0.053 [b] 0.003 ** [c] 0.562	0.166
12th week	−26.78 ± 17.91	−27.04 ± 8.16	−14.49 ± 13.78	0.002 ** [a] 0.023 * [b] <0.01 ** [c] 0.096	0.160
p	<0.01 **	<0.01 **	<0.01 **		
Baseline-6th week	[d] <0.01 **	[d] <0.01 **	[d] 0.017 *		
Baseline-12th week	[d] <0.01 **	[d] <0.01 **	[d] <0.01 **		

Results are expressed as mean ± standard deviation. *p*: one-way ANOVA test statistics *p* value (comparison of different columns) and repeated measures one-way ANOVA test statistics *p* value (comparison of time effect in the same column). *: $p < 0.05$, **: $p < 0.01$. Superscript letters a,b,c express *p* values of Post hoc Tukey's test results of one-way ANOVA test (comparison of different columns); [a]: comparison of differences in dextrose prolotherapy and exercise groups, [b]: comparison of differences in exercise and ozone groups, [c]: comparison of differences in prolotherapy and ozone groups. Superscript letter [d] expresses the *p* value of Bonferroni test result of repeated measures one-way ANOVA test (comparison of mean baseline, 6th week, and 12th week values in the same group). η2: eta-squared value of one-way ANOVA test between different groups.

TUG, ROM-active, and ROM-passive *p* results of all groups and comparisons of differences are given in Table 4.

Table 4. TUG and ROM scores of groups and comparisons.

TUG	Groups			*p*	η2
	Dextrose Prolotherapy (n = 25)	**Ozone Therapy (n = 25)**	**Home-Based Exercise Therapy (n = 25)**		
Baseline	11.83 ± 2.28	13.82 ± 2.55	12.55 ± 2.91	0.019 * [a] 0.591 [b] 0.157 [c] 0.016 *	0.094
6th week	−0.56 ± 0.90	−0.79 ± 0.72	−0.85 ± 1.36	0.588	0.082
12th week	−0.86 ± 1.19	−1.31 ± 0.82	−0.63 ± 1.30	0.102	0.067
p	0.030 *	<0.01 **	0.019 *		
Baseline-6th week	[d] 0.013 *	[d] <0.01 **	[d] 0.013 *		
Baseline-12th week	[d] 0.004 **	[d] <0.01 **	[d] 0.067		
ROM-active					
Baseline	126.0 ± 13.84	125.83 ± 9.96	129.80 ± 10.55	0.409	0.025
6th week	6.40 ± 7.84	4.80 ± 7.42	2.28 ± 4.99	0.109	0.006
12th week	9.40 ± 6.97	8.60 ± 6.04	3.80 ± 5.45	0.004 ** [a] 0.006 ** [b] 0.021 * [c] 0.891	0.009
p	<0.01 **	<0.01 **	0.006 **		
Baseline-6th week	[d] 0.01 **	[d] 0.01 **	[d] 0.095		
Baseline-12th week	[d] <0.01 **	[d] <0.01 **	[d] 0.006 **		
ROM-passive					
Baseline	133.68 ± 10.83	132.92 ± 9.88	136.32 ± 5.97	0.366	0.026
6th week	3.12 ± 5.66	3.20 ± 5.75	1.16 ± 3.81	0.291	0.006
12th week	3.32 ± 5.82	4.80 ± 6.37	1.88 ± 3.76	0.172	0.009
p	0.024 *	0.050*	0.058		
Baseline-6th week	[d] 0.033 *	[d] 0.031 *	[d] 0.425		
Baseline-12th week	[d] 0.026 *	[d] 0.003 **	[d] 0.060		

Results are expressed as mean ± standard deviation. *p*: one-way ANOVA test statistics *p* value (comparison of different columns) and repeated measures one-way ANOVA test statistics *p* value (comparison of time effect in the same column). *: $p < 0.05$, **: $p < 0.01$. Superscript letters a,b,c express *p* values of Post hoc Tukey's test results of one-way ANOVA test (comparison of different columns); [a]: comparison of differences in dextrose prolotherapy and exercise groups, [b]: comparison of differences in exercise and ozone groups, [c]: comparison of differences in prolotherapy and ozone groups. Superscript letter [d] expresses the *p* value of Bonferroni test result of repeated measures one-way ANOVA test (comparison of mean baseline, 6th week, and 12th week values in the same group). η2: eta-squared value of one-way ANOVA test between different groups.

One-way ANOVA test results of three groups revealed that the baseline VAS-rest score of OT (9.71 ± 0.55) was significantly higher compared to exercise and DPT groups (5.84 ± 2.70; 5.08 ± 2.06 respectively) ($p < 0.01$, $\eta2 = 0.513$). There were significant improvements in VAS-rest scores of prolotherapy and OT groups in the 6th week and 12th week and the exercise group in the 12th week. It is seen that exercise and DPT have a similar effect of reducing VAS-rest scores ($p > 0.05$). OT was the most appropriate method to reduce VAS rest scores in both in the 6th week ($p < 0.01$, $\eta2 = 0.217$) and 12th week ($p = 0.045$, $\eta2 = 0.108$) (Figure 3).

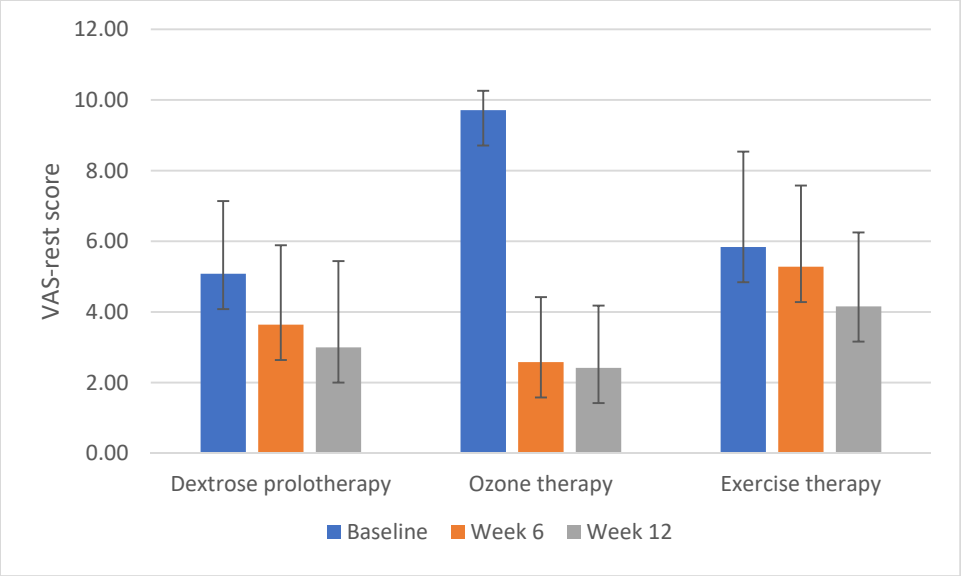

Figure 3. VAS-rest scores in dextrose prolotherapy, ozone therapy, and home-based exercise therapy groups.

WOMAC-function results were similar to WOMAC-total results. When we evaluate TUG, ROM-active, and ROM-passive scores, exercise therapy has reduced TUG scores in the 6th week compared to baseline, improved ROM-active scores in the 12th week compared to baseline, and no effect on ROM-passive scores.

Both OT and DPT have reduced TUG scores and improved ROM-active and ROM-passive scores in the 6th and 12th week compared to baseline. When we compare methods considering these parameters, OT and DPT were superior to exercise for improving ROM-active scores in the 12th week, but the effect size is minimal ($p = 0.004$, $\eta 2 = 0.009$). When we evaluate WOMAC-stiffness results, both OT and DPT were superior to exercise, and the most effective method was OT. OT was superior to HEP for reducing WOMAC-stiffness scores. When evaluating WOMAC-total scores it was seen that OT was superior to home-based exercise for reducing scores in the 6th week ($p = 0.003$, $\eta 2 = 0.166$); both DPT and OT were superior to exercise in the 12th week with a large effect size ($p = 0.023$ and $p < 0.01$, respectively; $\eta 2 = 0.160$), and both DPT and OT had similar effects (Figure 4).

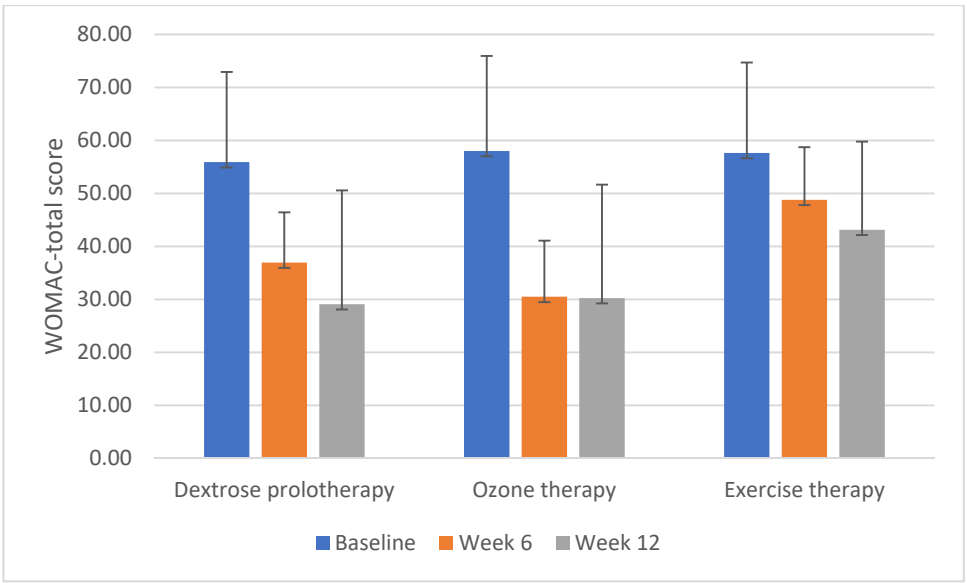

Figure 4. WOMAC-total scores in dextrose prolotherapy, ozone therapy, and home-based exercise therapy groups.

WOMAC-function results were similar to WOMAC-total results. When we evaluate TUG, ROM-active, and ROM-passive scores, exercise therapy has reduced TUG scores in the 6th week compared to baseline ($p = 0.013$) and improved ROM-active scores in the 12th week compared to baseline ($p = 0.006$) but showed no effect on ROM-passive scores.

Both OT and DPT have reduced TUG scores improved ROM-active and ROM-passive scores in the 6th and 12th week compared to baseline. When we compare methods considering these parameters, OT and DPT were superior to exercise for improving ROM-active scores.

4. Discussion

In the current study, DPT, OT, and home-based exercise therapy were applied to three groups of adult patients with symptomatic primary KOA, and the efficacy of the treatments was compared. DPT and OT were performed using both intraarticular and periarticular methods. The efficacy of treatments at week 6 and week 12 was compared with the baseline values. As a result of the study, all three treatment modalities showed positive effects on many outcome parameters. When the three methods were compared with each other, it was observed that in the 6th week, OT was more effective than DPT in two parameters (VAS-rest, VAS-movement) and more effective than the home-based exercise program in five parameters (VAS-rest, VAS-movement, WOMAC-stiffness, WOMAC-function, and WOMAC-total). In the 12th week, OT was more effective than DPT in three parameters (VAS-rest, VAS-movement, and WOMAC-stiffness) and more effective than the home-based exercise program in five parameters (VAS-rest, VAS-movement, WOMAC-stiffness, WOMAC-total, and ROM-active).

It is stated that home exercise programs in KOA patients are safe and effective, especially in terms of pain reduction and strength development. According to a systematic review evaluating the effectiveness of exercise programs in the treatment of KOA, exercise program implementation showed positive physical and functional results on at least one outcome variable [30]. In this study, it was observed that the home exercise program applied by the patients had positive effects on many parameters except ROM-passive at the 6th and 12th weeks in the treatment of KOA.

Many studies are investigating the use of DPT in the treatment of KOA and comparing the effectiveness of DPT with other treatment methods. The intraarticular dextrose concentration used in various studies ranges from 10% to 25%. The injection regime (number of injections, break durations, follow-up times) presents wide variations [17]. DPT has more beneficial effects than saline and home-based exercise therapies [27] and similar effects with PRP in reducing pain severity [26]. DPT can provide safe, significant, and sustained improvements in knee pain, function, and stiffness scores in adults with moderate-to-severe KOA [17]. In long term follow-up studies of DPT, the improvements in WOMAC scores were continued in week 52 [27] and year 2.5 [31].

The method of application is also an important determinant of the effectiveness of DPT. While no significant improvement was observed in WOMAC scores in a study in which DPT was applied via intraarticular and periarticular methods [26], significant improvements were observed in other studies [27,28]. A long-term follow-up study revealed that the positive effects of intraarticular and periarticular administration of DPT on WOMAC and pain scores continued at the 52-week control [31]. In addition, periarticular use of DPT alone is also effective in relieving KOA symptoms [32]. In this study, intraarticular and periarticular administration of DPT improved WOMAC scores. Our study supports the findings in the literature that intraarticular and periarticular use of DPT is effective in relieving KOA symptoms.

The current study showed significant improvements in DPT, ozone, and exercise groups in WOMAC scores of stiffness, physical function, and total, both at 6 weeks and 12 weeks, compared to baseline. Considering WOMAC total scores 47.8% of patients of the OT group, 47.9% of patients of the DPT group and 25.1% of patients of the HEP group showed significant improvements from baseline at week 12. The OT and DPT groups were more effective than the HEP group, but they were not superior to each other.

The use of OT in treatment of has become widespread in recent years [33,34]. OT application in KOA contributes to a decrease in pain intensity, disappearance of edema and increase in mobility. Although the mechanism of action is not fully known, OT has favorable effects on pain relief by decreasing oxidative stress, improving anti-inflammatory pathways and blood circulation [35]. However, there is no consensus in the studies regarding OT's injection side, volume, and concentration [33]. OT at the dose of 30 mcg/mL (20 mL) with the IA method effectively reduces the severity of pain in KOA patients [36]. Administration of OT at the dose of 30 mcg/mL (10 mL) with the IA method three times a week reduces pain intensity after 6 months. However, the decrease in pain intensity is not different from the decrease obtained with a home exercise program [37].

In several OT studies in KOA patients, VAS pain scores and WOMAC scores (pain, stiffness, physical function, and total) were improved significantly from baseline. The effect of three doses of OT was continued for 3 months [38] and for 6 months [37,39], the effect of eight doses of OT was 3 months [40], the effect of four doses of OT was decreased at 3 months and disappeared in 6 months [41], the effect of four doses of OT continued to the follow-up after 4 weeks [42], and the effect of 15 sessions OT (two sessions in a week) was continued to the follow-up after 12 months [20]. The comparison of the long-term effectiveness of OT, PRP, and hyaluronic acid applications in KOA patients showed a significant decrease in pain intensity at the end of the 1st month in the OT group, and the effects decreased at the 3rd month. It disappeared at the 6th month [41]. Therefore, the long-term effectiveness of ozone therapy is controversial. In the current study, ozone therapy continued its pain relieving effect (demonstrated with VAS-rest and VAS-movement) at the 12th week. Further studies are needed for the effects of ozone therapy longer than 12 weeks.

There is an only one available study in the literature comparing DPT and OT in the treatment of KOA. In the study mentioned above, KOA patients were divided into two groups, and IA 12.5% DPT was administered to one group and 15 g/mL of ozone/oxygen mixture (5–7 cm^3) OT was administered to the other group three times with 10-day intervals. After 3 months, pain intensity decreased in both groups, but there was no significant difference between the groups [38]. In the current study, 12.5% DPT and OT were applied to the same 10 points with both IA and PA injections, and results were compared with the exercise group considered as a control group. Pain intensity and WOMAC scores were significantly reduced in both DPT and OT groups at weeks 6 and 12, consistent with the literature. The reduction in all VAS scores at weeks 6 and 12 was more effective with ozone therapy than with prolotherapy. Again, the decrease in WOMAC-stiffness scores and VAS scores was more effective in the ozone group at the 6th and 12th weeks. In our study, the significant superiority of OT over DPT in reducing pain intensity and stiffness is probably due to the combination of OT using IA and PA injections.

The superiority of OT to DPT was shown with TUG scores. Both prolotherapy and ozone therapy decreased TUG scores at 6 and 12 weeks compared to baseline. When the difference between treatment groups was evaluated, it was seen that the therapeutic effect of ozone therapy on TUG scores was more effective than prolotherapy. Again, prolotherapy and OT improved ROM-active and ROM-passive scores, and prolotherapy and OT showed superiority over exercise therapy in improving ROM-active score. In one of the few studies in the literature evaluated with TUG, no difference was found between OT and placebo at week 12 [40]. Our findings are in line with this result. This study has a limitation: The patients were not blinded to which therapy they had been taken because we informed them of ethical issues.

5. Conclusions

This is the first study in which DPT and OT were administered as both IA and PA injections in patients with primary KOA. The short and medium effects of two different injections are compared with exercise, the primary treatment. Non-operative management of patients with KOA can be achieved by combining OT and DPT with a home exercise

program. In both injection techniques, the protocol is easy to learn and implement, and both injection techniques are cost-effective.

When the effectiveness of OT and DPT was compared, it was seen that OT was more effective than DPT on many outcome parameters. Intraarticular and periarticular OT application can be preferred in centers with technical infrastructure to improve pain and functional status in KOA patients. The long-term effects of both DPT and OT should be investigated in further studies.

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