Prolotherapy for knee osteoarthritis

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Background and aim Osteoarthritis (OA) is the most common type of chronic arthritis and represents a major cause of pain and disability. Prolotherapy is an injection of hypertonic dextrose used for painful chronic musculoskeletal pain conditions, including knee OA.

Patients and methods This study was done to evaluate the effect of prolotherapy in treatment of knee OA. It was carried out on 200 patients with mild to moderate knee OA. The patients were classified into two groups: group 1 (100 patients) was treated by prolotherapy at 1, 5, and 9 weeks with re-evaluation after 6 months, and group 2 (100 patients) was treated by NSAIDS and physiotherapy for 6 months and served as a control group.

Results The 6-month post-treatment visual analog scale and Western Ontario and McMaster Universities Osteoarthritis Index showed significant difference in pain, stiffness, and functional disability (P=0.001 and 0.043; 0.032 and 0.027; and 0.007 and 0.015, respectively) in both groups when compared with the baseline. However, on comparing both groups after treatment, we noticed significant difference in pain and disability favoring group 1 (P=0.031 and 0.048, respectively), whereas stiffness did not show significant difference between them (P=0.83). By knee ultrasound, degree of synovitis showed significant difference in groups 1 and 2 when compared with the baseline (P=0.004 and 0.007, respectively), but other parameters showed no significant differences. However, when comparing both groups after treatment, we noticed significant difference in cartilage thickness favoring group 1 (P=0.01), whereas other parameters did not show significant difference between them, although the degree, signs, and symptoms of knee effusion were improved in favor of prolotherapy group.

Conclusion Prolotherapy is a promising line for treatment of knee OA. Prolotherapy reduces pain and improves the functional status in patients with knee OA.

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Introduction

Osteoarthritis (OA) is the most common type of chronic arthritis and represents a major cause of pain and disability. The effect of current treatment is limited. Current guidelines suggest that the management of knee OA should include nonpharmacological, pharmacological, surgical, and complementary therapies [1].

There are limited accepted core sets for treatments of patients with knee OA, despite the efforts by the Osteoarthritis Research Society International. A safe and effective treatment option for knee OA remains a top priority in clinical practice and research. In the USA, assessment of knee OA treatment has been identified as a 'top 100' research priority by the National Academy of Medicine and the Agency for Healthcare Research and has called for new knee OA therapy [2].

Prolotherapy (hypertonic dextrose injection) is used for chronic musculoskeletal pain conditions, including knee OA. The practice principle of prolotherapy is injection of small volumes (0.5–6 ml) of hypertonic dextrose, at painful ligament, tendon attachments, and in adjacent joint spaces [3].

The mechanism of action of prolotherapy is unclear. Hypothesis suggests that prolotherapy stimulates local healing of chronically injured extra-articular and intra-articular tissue but definitive evidence is lacking [4].

Some searches reported improvement in outcomes in response to prolotherapy [5,6]. The aim of our work is to evaluate the effect of prolotherapy in treatment of knee OA.

Patients and methods

This is a prospective study in which 200 patients were selected randomly of both sex and different ages with knee OA grades I, II, III diagnosed according to the American College of Rheumatology criteria [7]. They provided informed consent for participation.

All the patients were recruited from Rheumatology Clinic, Al Azhar University Hospital, Damietta, Egypt between March 2017 and February 2018.

All the patients with chronic debilitating diseases (diabetes mellitus, chronic liver, renal diseases, cardiopulmonary diseases, cancers and the under nutrition) were excluded from our study. Moreover, secondary knee OA associated with autoimmune disease, gouty arthritis, hormonal imbalance, infection or hematological disorders and patients with morbid obesity and advanced knee OA grade IV were excluded as well.

The patients were classified into two groups: one group (100 patients) was treated by prolotherapy at 1, 5, and 9 weeks with re-evaluation after 6 months. The second group (100 patients) was treated by NSAIDS and physiotherapy for 6 months and served as a control group. The age, sex, and body mass were matched in both groups.

All patients were subjected to medical history taking, general examination, joint examination, and laboratory investigations to exclude conditions that may delay healing (complete blood count, erythrocyte sedimentation rate, C-reactive protein, aspartate aminotransferase, alanine aminotransferase, and albumin, serum creatinine, urine analysis, random blood sugar, serum uric acid rheumatoid factor and antinuclear antibody). All patients were assessed at baseline and 6 months later by visual analog scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), plain radiography of both knees, and musculoskeletal knee ultrasound (US).

Plain radiographs were obtained for both knees using the digital plain radiographic machine. The anteroposterior view in standing position was taken to evaluate the medial and lateral joint spaces, the lateral view for evaluation of the patella-femoral joint and the skyline (sunrise) view for more information about the joint space.

According to Kellgren–Lawrence Classification, grading of the knee OA was done: normal, grade I, grade II, grade II, and grade IV [8].

Grade I: no joint space narrowing and no possible osteophytes.
Grade II: possible narrowing of the joint space and small osteophytes.
Grade III: multiple, moderate-size osteophytes, definite joint space narrowing, some sclerotic areas and possible deformity of bone ends.
Grade IV: multiple, large osteophytes, marked narrowing of the joint space, marked sclerosis, and definite deformity of bone ends.

Musculoskeletal US was done for each knee using a four-dimensional diagnostic high-resolution US machine equipped with high-frequency transducer adjusted at 6–10 MHz.

US Doppler examination was performed on the affected knee before and after 6 months for detection of cartilage degeneration of the osteoarthritic knee [9].

Patients were kept supine, with knee flexed as much as possible while underlying a rolled towel or pillow for much comfort of the patient.

US reports included comment on the following:

Effusion: maximal depth was measured in millimeters and marked as abasement if less than 4 mm and presence if more than or equal 4 mm [10].
Synovial thickness (hypertrophy): area of thickened synovium was scanned and the increased signal was scored using a semiquantitative system, with grades 0–3 [11].
Cartilage thickness and regularity [12].
Joint space was measured.

The dimensions [length, width, and cross-section (mm)] were recorded for each medial collateral ligament, lateral collateral ligament, and patellar tendon. The thickness of the articular cartilage (mm) was recorded for the medial and lateral articular compartments.

Classic prolotherapy technique: according to Hackett [13], the knee joint was sterilized with alcohol 70% and betadine. The tender knee locations were marked with a new eye-brow pencil. Anesthetic skin wheals were placed with 1% lidocaine. Periarticular and intra-articular injections were performed according to Table 1.

All the patients were advised to apply hot foments to their knees at home and to do massage in between the sessions to decrease the pain and to increase the blood circulation which improves the healing process [14].

They were discouraged from using NSAIDs and advised to decrease their activities [6].

According to Hauser and Hauser [15] and Rabago *et al.* [6], all patients were taught knee exercises to start 2 days after the injection session at-home, to begin with three sessions per week, one repetition per day, 10 repetitions per exercise; to gradually increase it as tolerated over 25 weeks (five sessions per week, three times per day, 15 repetitions per exercise); and to continue them thereafter till the end of the study.

Table 1 Injection technique of prolotherapy

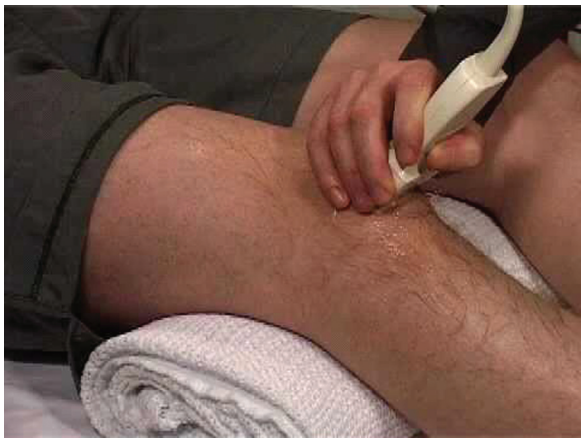
Injection site	Solution	Injection technique
Intra-articular	25% dextrose (8 ml) and 2% lidocaine (2 ml)	10 ml was injected using an anteromedial or anterolateral approaches
Periarticular injection	25% dextrose (8 ml) and 2% lidocaine (2 ml)	Up to 15 subdermal injections of 0.5 ml of solution was injected with a 25 G, 2¾ inches needle at each ligament-bone insertion site. Injection occurs along the MCL, LCL, PESancerin, around the patella and any other painful point

MCL, medial collateral ligament; LCL, lateral collateral ligament.

Statistical analysis

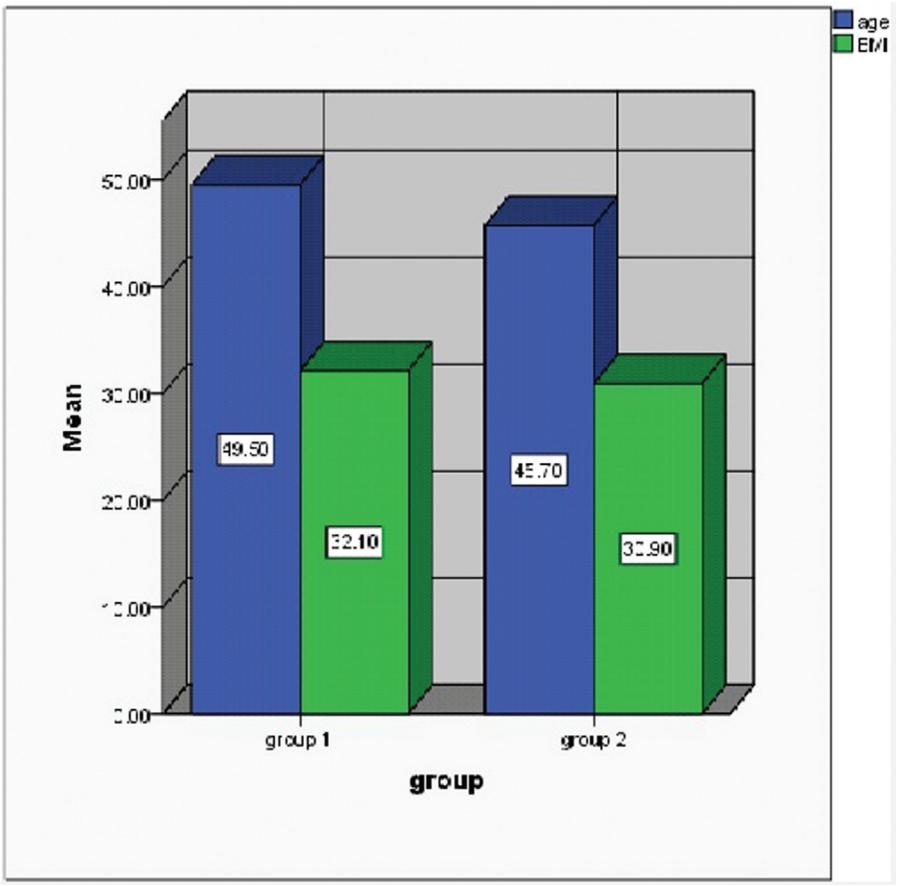
Data entry and statistical analysis were performed using statistical package for the social sciences, version 21 (SPSS Inc., Chicago, Illinois, USA) by Baron and Kenny [16]. Categorical data were expressed in number and percentage. Continuous normally distributed data were

Figure 1



Measuring the dimensions of the right knee joint using US. US, ultrasound.

Figure 2



Mean age and BMI among patients in both group.

expressed in mean and SD. The quantitative data were examined by Kolmogorov–Smirnov test for normality of data [17].

Student's *t* test was used for continuous normally distributed data. Comparison of categorical data was done using χ^2 test or Fisher exact test used whenever appropriate.

Statistical significance was considered when *P* value was less than or equal to 0.05. The relative risk (odds ratio) for each genotype and minor allele was estimated with a 95% confidence interval and calculated by binary logistic regression analysis.

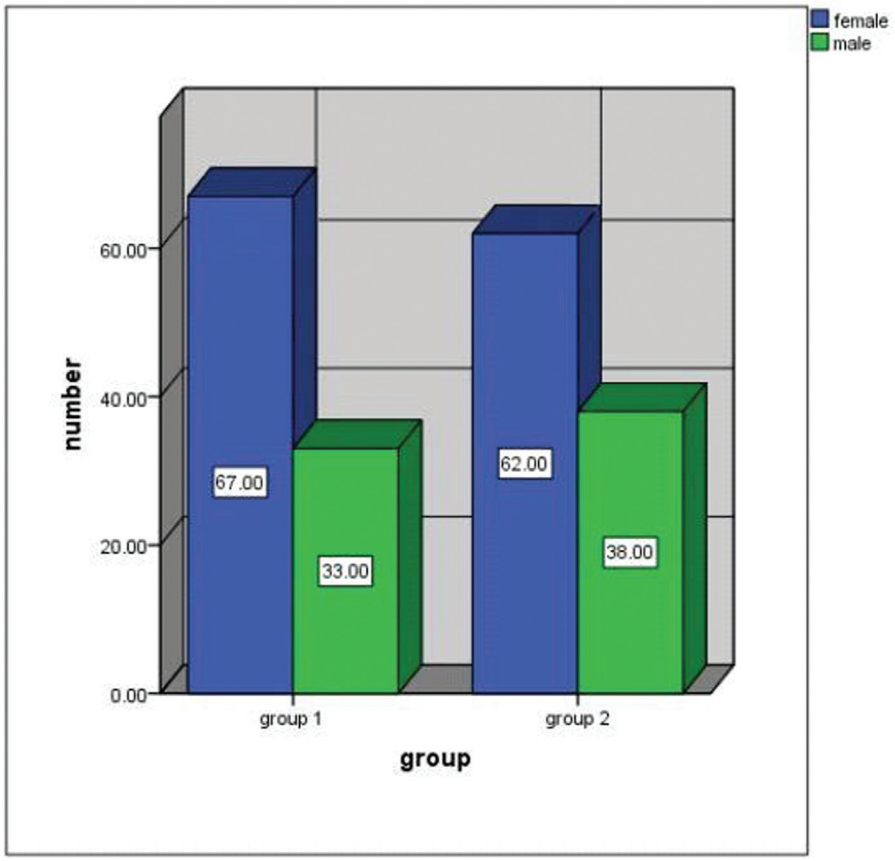
Results

The patients in group 1 comprised 33 male and 67 female, but in group 2, there were 38 male and 62 female. This comes to an observation that the incidence of OA among female may be greater than male. The patients were of any age (Figs 1–12).

According to radiological evaluation of knee joint at baseline, patients were classified into three grades (I, II, and III OA). Group 1 included 14 patients with grade I, 77 patients with grade II, and nine patients with grade III, whereas group 2 included 19 patients with grade I, 75 patients with grade II, and 16 patients with grade III (Fig. 4).

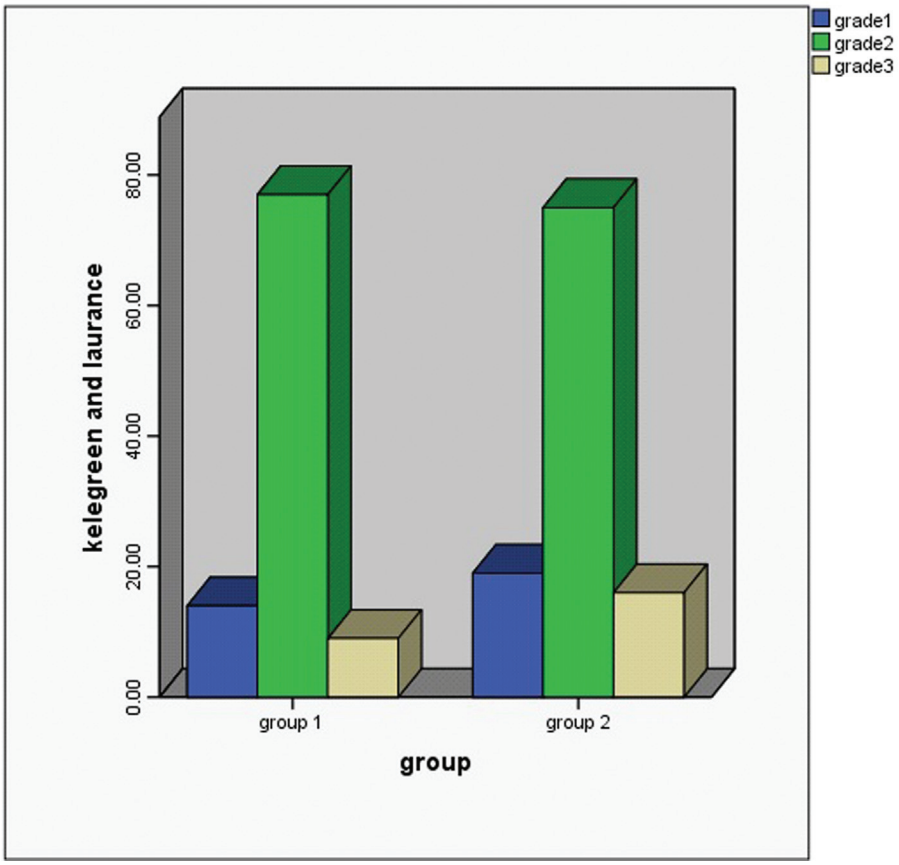
In this study, VAS and WOMAC scores were obtained at baseline and 6 months later. At baseline, both groups had the same VAS and WOMAC scores, with no significant differences in pain, stiffness, and functional disability (*P*=0.213, 0.772, and 0.509, respectively). Six months after treatment, VAS and WOMAC showed significant difference in pain, stiffness, and functional disability (*P*=0.001 and 0.043; 0.032 and 0.027; and 0.007 and 0.015, respectively) when both groups were compared with the baseline. However, when comparing both groups after treatment, we noticed a significant difference in pain and disability favoring group 1 (*P*=0.031 and 0.048, respectively), whereas stiffness did not show significant difference between them (*P*=0.83), although both groups showed clinical improvement as stiffness mean was 2.3±1.01 and 2.8±0.4 and became 2.1±0.9 and 2.2±0.6 in groups 1 and 2, respectively (Table 2).

Figure 3



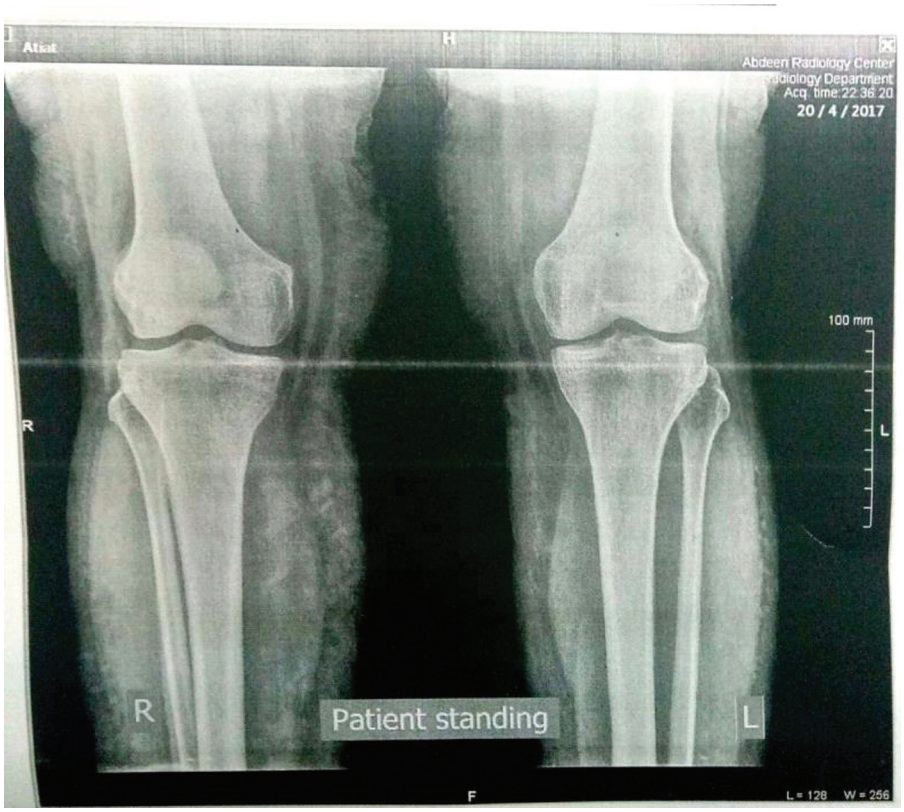
Sex among patients in both groups.

Figure 4



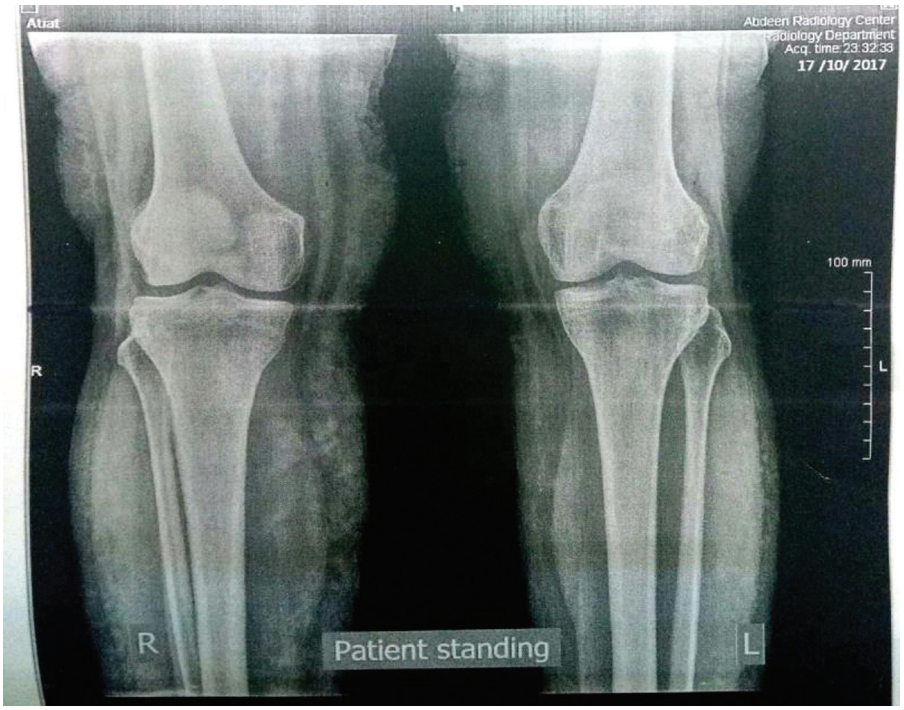
Radiological evaluation by Kellgren–Lawrence staging.

Figure 5



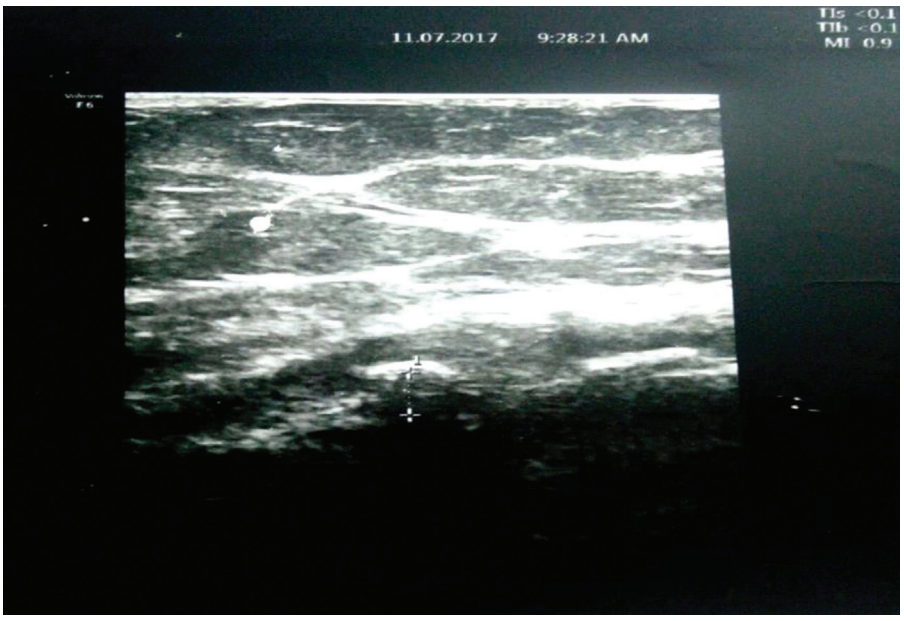
Plain radiography anteroposterior standing view for female patient before prolotherapy.

Figure 6



Plain radiography anteroposterior standing view for previous patient 6 months after prolotherapy.

Figure 7

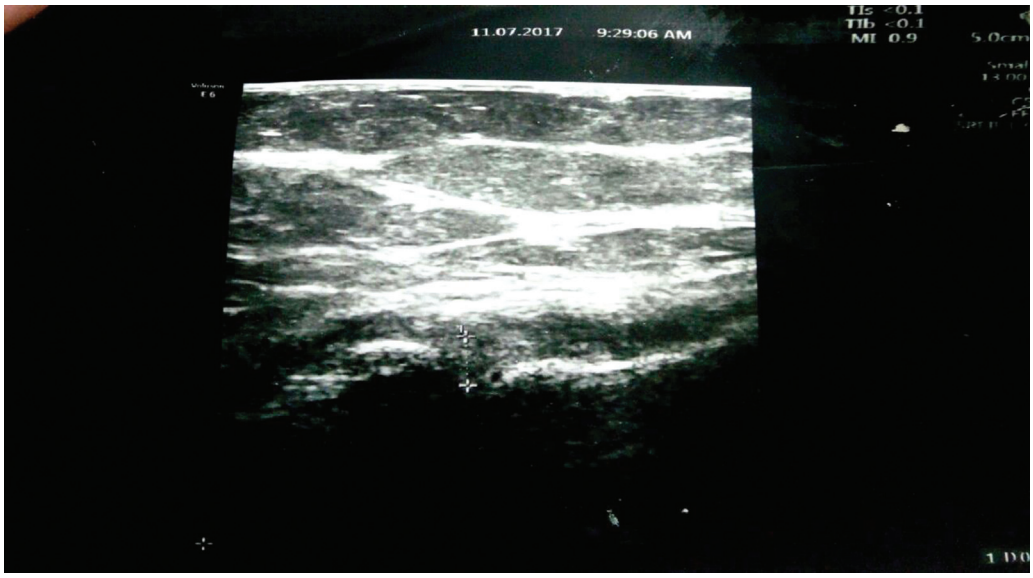


Showing knee US of female patient, 58 years old with knee OA grade II, done before prolotherapy. OA, osteoarthritis. US, ultrasound.

Moreover, knee US was done at baseline and 6 months later. At baseline, both groups are the same in degree of synovitis, cartilage thickness, joint space narrowing, and effusion, with no significant differences between them (*P*=0.671, 0.561, 0.877, 0.321, respectively). Six months after treatment, only the degree of synovitis showed significant difference in groups 1 and 2 when compared with the baseline (*P*=0.004 and 0.007, respectively), but other parameters showed no significant differences.

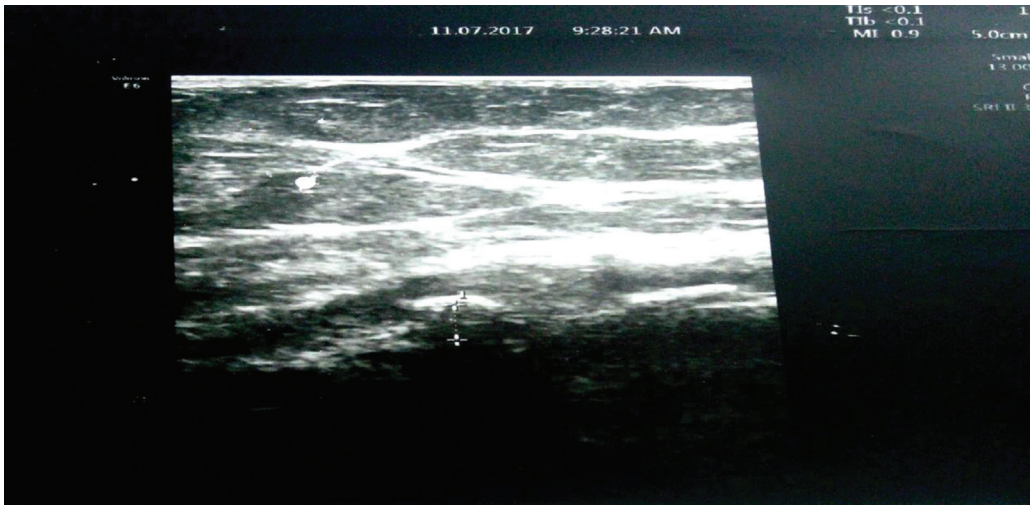
However, when comparing both groups after treatment, we noticed significant difference in cartilage thickness favoring group 1 (*P*=00.01), whereas other parameters did not show significant difference between them, although the degree, signs,

Figure 8



Showing knee US of female patient, 58 years old with knee OA grade II, done before prolotherapy. OA, osteoarthritis; US, ultrasound.

Figure 9



Showing knee US of a 58-year-old female patient with knee OA grade II, done before prolotherapy. OA, osteoarthritis; US, ultrasound.

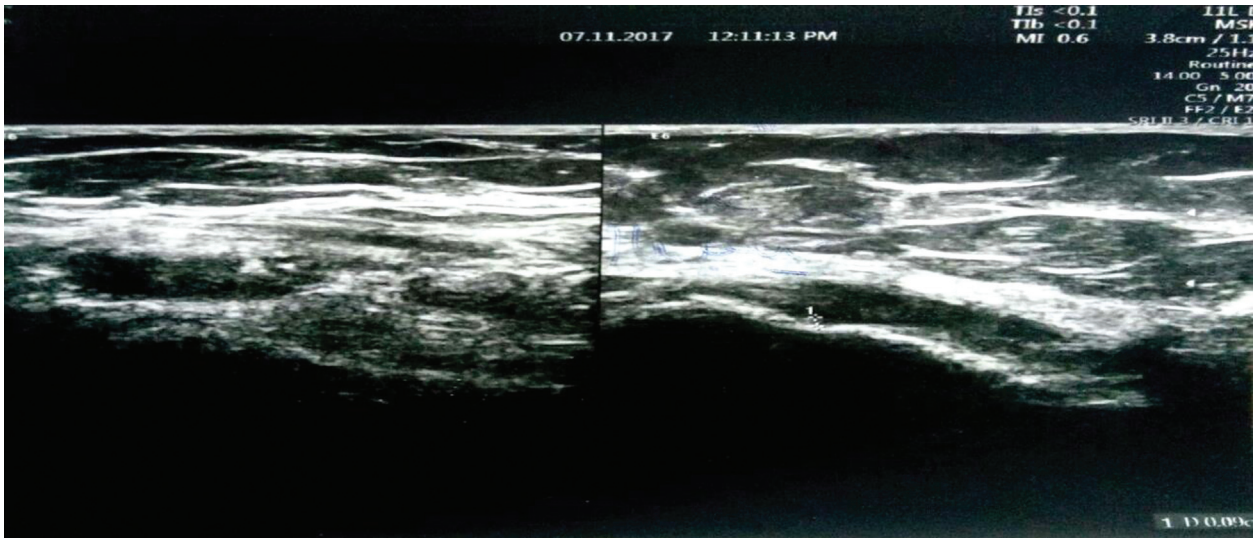
and symptoms of knee effusion were improved in favor of prolotherapy group (Table 3).

Plain radiography of knee joint did not show significant difference between both groups before treatment and 6 months after treatment, and it is recommended to be repeated after 1 year.

Discussion

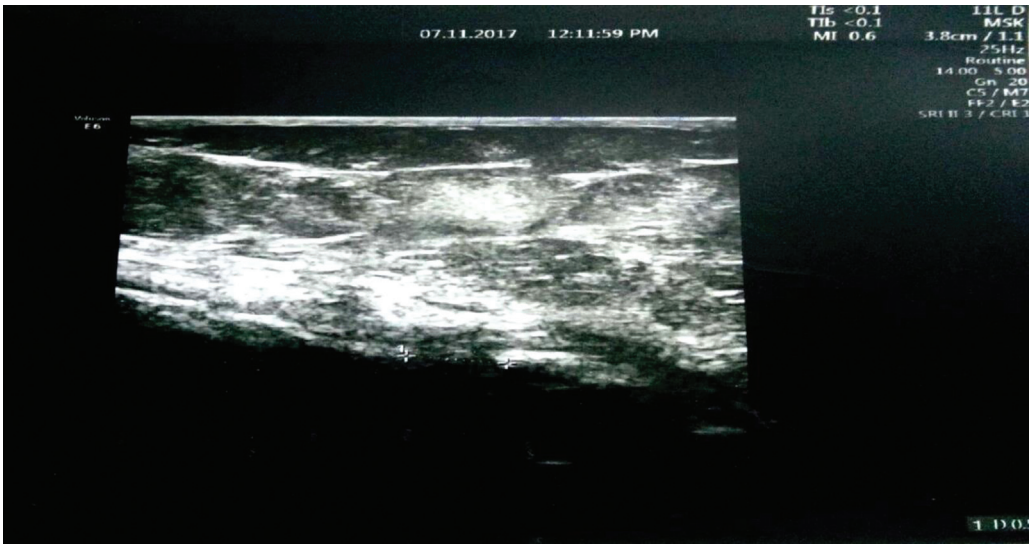
This study was done to evaluate the effect of prolotherapy in treatment of knee OA. The study was carried out on 200 patients with mild to moderate knee OA. The patients were classified into two groups: group 1 included 100 patients treated by prolotherapy at 1, 5, and 9 weeks with re-evaluation after 6 months, and group 2 included 100 patients treated by NSAIDS and physiotherapy for 6 months and served as a control group. Six months after treatment, VAS and WOMAC showed significant difference in pain, stiffness, and functional disability (P=0.001 and 0.043; 0.032 and 0.027; and 0.007 and 0.015, respectively) in both groups when compared with the baseline. However, on comparing both groups after treatment, we noticed significant difference in pain and disability favoring group 1 (P=0.031 and 0.048, respectively), whereas stiffness did not show significant difference between them (P=0.83), although both groups showed clinical improvement as

Figure 10



Showing knee US of the previous patient, done 4 months after prolotherapy. US, ultrasound.

Figure 11



Showing knee US of the previous patient, done 4 months after prolotherapy. US, ultrasound.

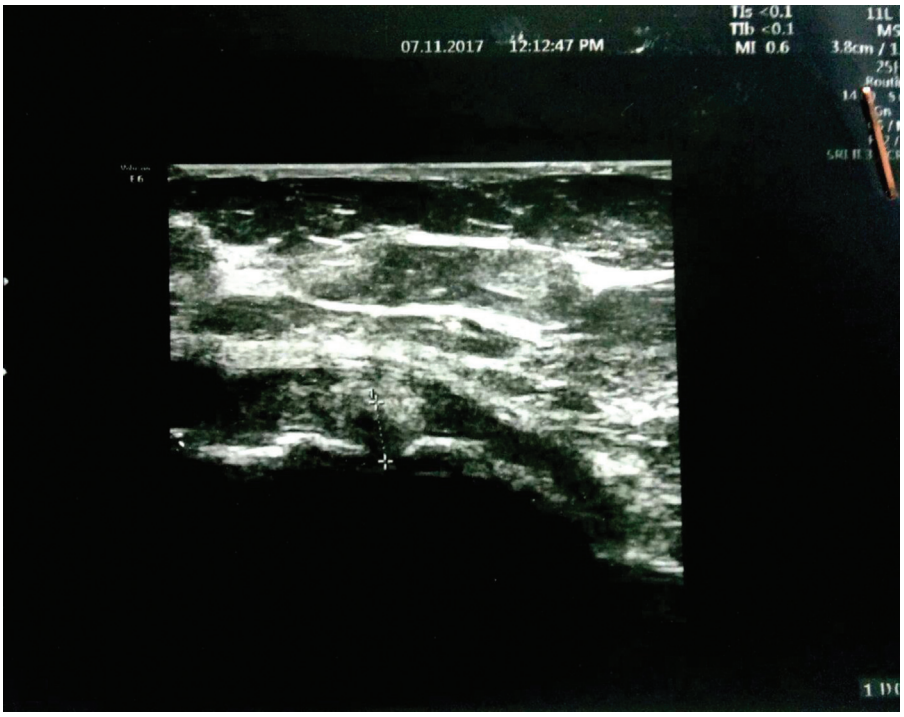
stiffness mean was 2.3±1.01 and 2.8±0.4 and became 2.1 ±0.9 and 2.2±0.6 in groups 1 and 2, respectively.

On knee US, 6 months after treatment, only degree of synovitis showed significant difference in groups 1 and 2 when compared with the baseline (P=0.004 and 0.007, respectively), but other parameters showed no significant differences.

However, on comparing both groups, we noticed significant difference in cartilage thickness favoring group 1 (P=00.01), whereas other parameters did not show significant difference between them, although the degree, signs, and symptoms of knee effusion were improved in favor of prolotherapy group. Our results, agree with Rabago and colleagues that compared the effect of prolotherapy on 90 adults with at least 3 months. Prolotherapy was done at 1, 5, and 9 weeks with as-needed additional treatments at weeks 13 and 17. We used the same intervals in our trial, and we had the same inclusion and exclusion criteria.

However, they used only dextrose 25% as an injected solution and anesthesia for the skin by lidocaine 1%, but in our trial, we used both dextrose 25% and lidocaine 2% as injected solutions, so we did not

Figure 12



Showing Knee US of the previous patient, done 4 months after prolotherapy. US, ultrasound.

Table 2 Clinical evaluation before treatment and after treatment by Western Ontario and McMaster Universities Osteoarthritis Index and visual analog scale

WOMAC	Groups	Before treatment (mean±SD)	–After treatment (mean±SD)	*P*
VAS (mean±SD)	Group 1	7.2±1.05	2.5±1.2	0.001*
	Group 2	6.9±2.1	5.3±1.8	0.043*
P		0.213	0.031*	
Stiffness (mean±SD)	Group 1	2.3±1.01	2.1±0.9	0.032*
	Group 2	2.8±0.4	2.2±0.6	0.027*
P		0.772	0.83	
Functional disability (mean±SD)	Group 1	16.4±3.4	12.7±4.9	0.007*
	Group 2	17.3±2.8	14.5±3.3	0.015*
P		0.509	0.048*	
Total (mean±SD)	Group 1	23.3±7.2	18.4±6.1	0.001*
	Group 2	24.4±6.1	20.2±5.3	0.009*
P		0.669	0.045*	

VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index. *significant

need pain killers after injection as they needed. Moreover, they used VAS, WOMAC, and radiograph with anteroposterior standing position in the assessment, as in our trial, but we added musculoskeletal knee US.

Rabago *et al*. [18] showed approximately similar results to ours, where there were no baseline differences existed between both groups, and all groups reported improved composite WOMAC scores compared with baseline status ($P<0.1$) after 52 weeks. Adjusted for sex, age, and BMI, WOMAC scores for patients receiving dextrose prolotherapy improved more ($P<0.5$) at 52 weeks than did scores for patients received saline and exercise and exceeded the WOMAC-based minimal clinically important difference. Individual knee pain scores also improved more in the prolotherapy group ($P=0.5$).

Moreover, in agreement with our results, another randomized clinical trial by Hashemi *et al*. [19], showed the effects of prolotherapy versus intra-articular ozone (prolozone) in patients with mild to moderate knee OA, and this trial was done on 80

Table 3 Knee ultrasound evaluation before and after treatment

Knee ultrasound	Group	Before treatment	After treatment	*P*
Cartilage thickness (mean±SD)	Group 1	4.5±1.19	5.2±1.01	0.171
	Group 2	5.4±2.1	5.6±1.1	0.655
P		0.561	0.001*	
Synovial thickness (mean±SD)	Group 1	1.3±0.5	0.8±0.2	0.004*
	Group 2	1.2±0.4	0.9±0.3	0.007*
P		0.671	0.062	
Joint space (mean±SD)	Group 1	7.5±1.8	8.5±1.9	0.239
	Group 2	7.8±2.1	8.2±1.3	0.709
P		0.877	0.704	
Effusion [*n* (%)]				
No	Group 1	8 (8)	16 (16)	0.352
Minimal		16 (16)	32 (32)	
Mild		60 (60)	52 (52)	
Moderate		16 (16)	0 (0)	
No	Group 2	11 (11)	28 (28)	0.115
Minimal		34 (34)	33 (33)	
Mild		45 (45)	32 (32)	
Moderate		20 (20)	7 (7)	
P		0.312	0.076	

patients with mild to moderate knee OA, with the same inclusion and exclusion criteria as we did, except they used patients with OA grades I and II only, but we used also grade III, and they also used patients aged 40–75 years only, but we did not specify the age. Moreover, in their trial, they used VAS, WOMAC, and radiograph with anteroposterior standing position in the assessment, as in our trial, but we added musculoskeletal knee US.

Hashemi *et al.* [19] randomly assigned patients equally into two groups: ozone group and prolotherapy group. Before the prolotherapy, 1% lidocaine was injected as a local anesthetic to the skin and underlying tissues and the injections were repeated three times with 7–10 days interval for each patient. Three months after the last injection, the pain intensity was measured, and the WOMAC scores were determined. Finally, the pretreatment and post-treatment outcomes were compared in each group and between the two groups, but in our trial, the interval between the injections was at 1, 5, and 9 weeks and assessment after 6 months by using VAS, WOMAC, plain radiography, and musculoskeletal knee US.

Hashemi *et al.* [19] showed approximately similar results to ours, where they showed no statistically significant difference in pain and WOMAC between the two groups before treatment, but after treatment, there were significant improvements in pain and function in both groups, but no significant statistically difference between them.

Moreover, in agreement with our results, another study done by Eslamian and Amouzandeh [20], 2015, aimed to determine the efficacy of prolotherapy on pain, range of motion, and function in patients with moderate knee OA, with same inclusion and exclusion criteria, except they used patients with OA grades I and II only, and patient aged 45–75 years only.

In this study, the injected solution was 8 ml of 25% dextrose and 2 ml lidocaine 1% at baseline and then at 4 and 8 weeks, and the patient undergoes follow-up for 24 weeks. The diagnosis and follow-up was by plain radiography of the knee, and clinical data by VAS, WOMAC, and ROM, but we added musculoskeletal knee US that shows degree of synovitis, effusion, cartilage thickness, knee joint space, ACL, and PCL.

Eslamian and Amouzandeh [20], showed results which went with ours, as a total of 24 female patients (mean age, 58.37±11.8 years old) received 3-monthly injection therapies. Before the treatment, the mean articular range of motion was 105.41±11.22°. Mean VAS scale at rest and activity was 8.83±1.37 and 9.37 ±1.31, respectively. At the end of week 24, knee ROM increased by 8°. Pain severity in rest and activity decreased to 4.87±1.39, 45.86, and 44.23%, respectively ($P<0.001$). Total WOMAC score and its subcategories showed a continuous improvement trend in all the evaluation sessions, so that at the end of the study, the total score decreased by 30.5±14.27 points (49.58%) ($P<0.001$). Improvements of all parameters were considerable until week 8, and were maintained throughout the study period.

Our trial differed from others by using injected solution formed from dextrose 25% and lidocaine 2%, so our patients did not need pain killer after injection .We also introduced musculoskeletal knee US in assessment of knee OA, which showed significant difference in cartilage thickness favoring group 1 (P=00.01), when we compared both groups after treatment. So from our study, we can confirm that prolotherapy affects the function and structure of knee joint in patients with knee OA.

This may be explained by the study by Yoshii *et al*. [21,22] at 2009 and 2014 that confirmed that prolotherapy resulted in fibroblast and vascular proliferation, dense collagen deposition, and increase in ligament thickness.

Moreover, our results may be explained by the study by Park *et al*. [23] on animal model that suggested cartilage-specific anabolic growth as a result of intra-articular dextrose injection. Vora *et al*. [24] hypothesized mechanisms for pain relief included the following: (a) stimulation of local healing among chronically injured extra-articular and intra-articular tissue; (b) reduction of joint instability through the strengthening of stretched or torn ligaments; and (c) stimulation of cellular proliferation.

From all the previous trials in addition to ours, we can say that prolotherapy is a useful and fruitful method in the treatment of chronic knee OA, and we recommend that prolotherapy injection need to be more investigated on more patient as a safe and effective line of management of mild to moderate knee OA [24].

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Nil.

Conflicts of interest
There are no conflicts of interest.

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