

Comparative effectiveness of intra-articular prolotherapy versus peri-articular prolotherapy on pain reduction and improving function in patients with knee osteoarthritis: A randomized clinical trialHamid Reza Farpour¹, Farzane Fereydooni²

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Type of article: Original**Abstract**

Background: Osteoarthritis is a common degenerative disease. Prolotherapy is an alternative therapy used in multiple musculoskeletal disorders.

Objective: To compare the effectiveness of intra-articular dextrose injection versus peri-articular prolotherapy in patients with knee osteoarthritis (KOA).

Methods: Fifty-two adults with painful primary knee osteoarthritis for at least three months were randomized to intra- and peri-articular injection groups. Prolotherapy was done twice with two week intervals. The outcome measures included the Oxford Knee Scale (OKS), Western Ontario McMaster University Osteoarthritis Index (WOMAC), and Visual Analogue Scale (VAS), which were obtained from patients before the first injection at the base line and after the second injection at the fourth and eighth weeks.

Results: There were no statistically significant differences between demographic characteristics; before the injection, pain intensity, OKS, and WOMAC scores were approximately equal between the two groups. After dextrose prolotherapy, VAS, OKS, and WOMAC scores improved from baseline through the fourth and eighth weeks in both groups without any superiority between the two methods of injections ($p < 0.001$).

Conclusion: Dextrose prolotherapy either intra- or peri-articular injection resulted in significant improvement, so it could be an inexpensive and effective management of knee osteoarthritis.

Trial registration: The study protocol was registered as a clinical trial under registration ID of IRCT2016091229795N1 at the Iranian Registry of Clinical Trials (<http://www.irct.ir>).

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1. Introduction

Knee osteoarthritis in the elderly population is a common degenerative disease that imposes major economic burdens on the government and patient. Pain is the most common complaint that forces patients to seek treatment. Many structures could be the source of pain, involving the joint capsule, ligaments, and tendons (1-3). Depending on the severity of the disease, various therapeutic choices could be indicated, ranging from conservative management to surgical techniques (4, 5). Nonsurgical treatment is a multidimensional approach, which includes oral analgesia, physical therapy, multiple kinds of injections, etc. (6, 7). Prolotherapy is an alternative therapy that was first used in 1950 (8). The word “prolotherapy” is derived from “proliferation” (9). Hypertonic dextrose is a usual substance in prolotherapy (10). The mechanism of the dextrose is not understood well. One hypothesis is that dextrose causes an inflammation in the patients’ cells and initiates the inflammatory cascade. Also, it increases the growth factors and cytokines, which improve soft tissue healing and joint function (11). Dextrose stimulates regeneration of the joint

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cartilage. Some evidence supports the effect of prolotherapy on maturation of the fibrous tissue and the collagen fibers around and within the injured ligaments. Until now, conventional therapy for pain in KOA has not been effective; some, such as anti-inflammatory drugs and corticosteroids, have several side effects; others, such as platelet-rich plasma and hyaluronic injections, are expensive. Intra-articular injections also have serious complications such as septic arthritis. Dextrose prolotherapy could be used as an inexpensive, complementary treatment to decrease pain. Side effects related to dextrose injection such as bruising and post-injection pain are benign and temporary (12). However, a recent systematic review reported that dextrose prolotherapy was more effective than exercise and local anesthetic injection (13). To the best of our knowledge, there are not enough surveys on comparisons between peri- and intra-articular dextrose injections, so we designed this study to compare the effectiveness of intra- and peri-articular dextrose prolotherapy on decreasing pain and improving functions of patients with knee osteoarthritis.

2. Material and Methods

2.1. Trial design

This study was a double-blinded, randomized clinical trial in which we used a parallel design. Participants were selected from patients referred to physical medicine clinics from August 2016 to December 2016. The consort flowchart for selection, allocation and analysis is illustrated in Figure 1.

2.2. Participants

Participants were selected from patients referred to Shahid Rajaei and Emam Reza clinics, which are academic centers affiliated to Shiraz University of Medical Sciences (SUMS).

2.3. Selection criteria

The inclusion criteria were patient's age of 38-70 years old of both sexes; being diagnosed with knee osteoarthritis according to clinical criteria of the American College of Rheumatology (14); having grade 2 and 3 based on the Kellgren-Lawrence grading scale (15); complaining of pain, crepitation, and knee joint stiffness continuing for at least three months before the study. The VAS score should be 3 or more (16). The exclusion criteria were any infection involving the knee skin such as cellulitis, any intra- or peri-articular injection during the three last months, history of diabetes mellitus, rheumatological or inflammatory disease involving the knee joints, prior total knee arthroplasty, BMI more than 42, history of knee trauma or fracture during the three last months, history of acute lumbosacral radiculopathy or peripheral neuropathy, history of cancer, bleeding disorders, and pregnancy.

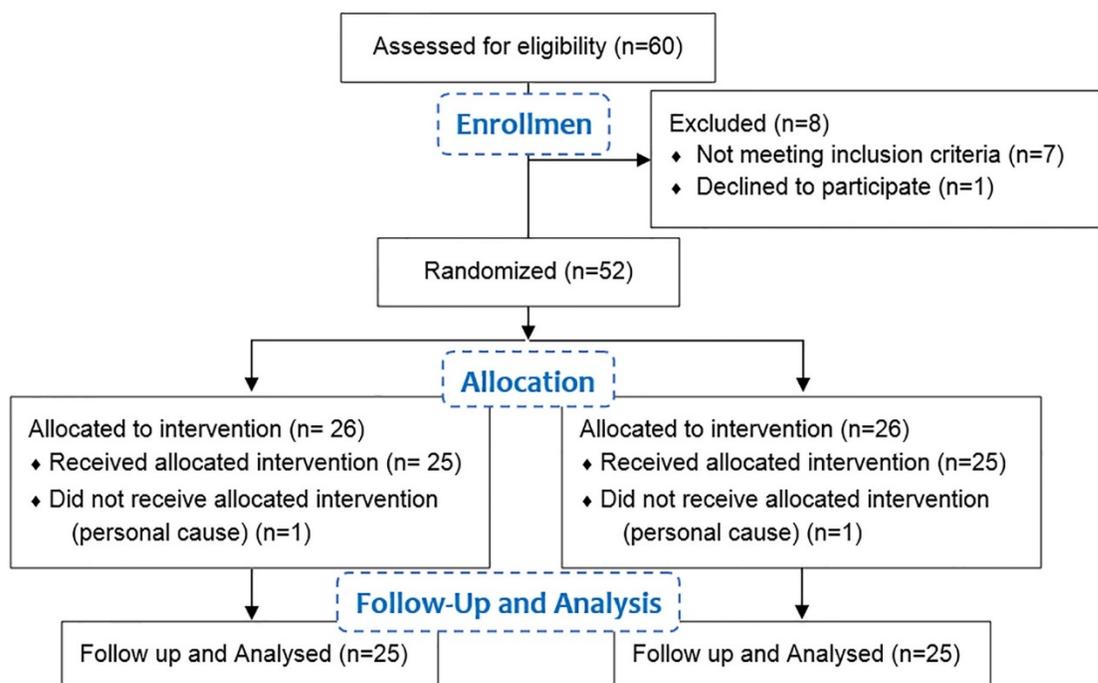


Figure 1. Consort flowchart of the trial

2.4. Intervention

Injections were performed for both groups on the first day and repeated two weeks later. In both groups, the patients were placed in a supine position with the 10°-15° knee flexion. In the peri-articular group, an expert physiatrist examined the knee and marked tender points around the knee up to three points. In this method, 6 milliliters of the dextrose 25% were injected totally. We used a 25 G needle to the subcutaneous tissue; then we brought the needle to just below the skin and redirected it in a new direction (fan shape) and repeated this protocol two to three times; 2 milliliters of the solution were injected in each tender point. In the intra-articular group, 6 milliliters of dextrose 25% were injected with inferolateral approach under sterile conditions. After injections, both groups were advised to hold an ice pack for 5 minutes on the injection sites three times a day for two days. We prescribed an acetaminophen tablet (325mg) if the patient had post-injection pain every 6 hours for 24 hours. Patients were asked to have relative knee rest for three days with progressive performance of daily activities over one month; also, the patients were encouraged to do quadriceps setting exercises and modify their lifestyle. They were advised to avoid anti-inflammatory drugs or other therapies for knee osteoarthritis.

2.5. Outcomes

Baseline demographic criteria included age, BMI, and sex. Pain intensity was measured with 10 degrees. We used the Visual Analogue Scale (VAS), in which 0 means no pain and 10 means worst possible pain. The other questionnaire was Western Ontario and McMaster Universities arthritis index (WOMAC), which evaluated the patient's function and consisted of three domains: pain (five items), stiffness (two items), and physical function (17 items) (17). The last questionnaire was the Oxford knee scale (OKS), which consisted of 12 questions with 0–5 ordinal scale (18). In both WOMAC and OKS, each answer had five ordinal scales (none=0, mild=1, moderate=2, severe=3, extreme=4). Also, both OKS and WOMAC are valid and reliable instruments for evaluating the OA of knee pain in Iran. The WOMAC, VAS, and OKS data were obtained from the patient before the first injection at the baseline and four and eight weeks after the second injections. The patients were visited by a second colleague who was not aware of the groups and filled the questionnaires. Also, they were asked to mention any reaction and side effect.

2.6. Sample size

The sample size was determined by considering a significance level of 0.5, power of 0.80, and probable dropout rate of 20%. The sample size was approximated to be 25 patients in each group.

2.7. Randomization and blinding

We randomly allocated 52 eligible subjects to two parallel groups (intra-articular injection: group A, and peri-articular injection: group B) by the administrator of the clinic who had been educated by using a block randomization list. The list was made by computer as a nonstratified list with the block size of four. The patients were not aware of being allocated in group A or B. Also, statisticians were kept blind about the allocation.

2.8. Statistical method

Demographic characteristics are demonstrated as mean ± standard deviation (continuous data). The statistical analyses consisted of chi-square, repeated measure ANOVA, t-test, and paired t-test; a p-value less than 0.05 was considered significant. For all analyses, we used the Statistical Package for the Social Science, version 18.0 (SPSS Inc., Chicago, IL, USA).

2.9. Ethics

The study method was approved by the Medial Ethics Committee of Shiraz University of Medical Sciences (SUMS) with the reference number "ir.sums.med.rec.1395.33" on July 26, 2016. The aim of the study was to describe orally to all participants before they participated in the study. Also, the researcher obtained written informed consent. The enrollment of patients initiated on August 2016, and the trial continued until December 2016. The study protocol was registered as a clinical trial under registration ID of IRCT2016091229795N1 at the Iranian Registry of Clinical Trials (<http://www.irct.ir>). The aim of the study was to describe orally to all participants before they participated in the study. The researcher obtained written informed consent. The patients were free to leave the study at any time; participation in the study was voluntary. Methods and design were not changed after we commenced the trial. If any complication occurred during the study, the researcher will follow up and treat the patients completely. Although to prevent any problem for patients, we recommended isometric quadriceps setting exercise, life-style modification, and prescribed acetaminophen if there was post-injection pain.

3. Results

In this study, from August 2016 to December 2016, a total of 60 patients were assessed, and 52 patients had eligibility criteria. They were randomized in two groups; finally, 25 patients participated in the trial in each group (Figure 1).

The baseline characteristics of patients are presented in Table 1. There were no statistically significant differences among demographic characteristics, pain intensity, OKS, and WOMAC scores; before the injections between the two groups. Table 2 shows the VAS and OKS outcomes. Baseline VAS scores were 7.32±1.46 in peri-articular and 7.80±1.70 in intra-articular that, after dextrose prolotherapy, improved through the fourth and eighth weeks (5.48±1.91, 5.00±2.27 in peri-articular group and 6.40±2.17, 5.90±2.69 in intra-articular group). Also, OKS score improved after treatment in both groups. Patients that were treated with peri-articular injection had 23.52±7.77 versus 24.72±7.13 scores in intra-articular injection. OKS increased in both groups through the fourth and eighth weeks (peri-articular: 27.44±8.98, 28.36±9.62, intra-articular: 25.52±8.51, 27.76±8.67). Similar to OKS and VAS, the total WOMAC score improved from baseline (46.52±14.19 and 45.68±11.18, peri- and intra-articular respectively) through the fourth and eighth weeks of follow up (peri-articular: 38.60±16.2, 36.44±16.2 and intra-articular: 41.16±13.66, 39.36±14.88), WOMAC subscales are presented in Table 3.

Table 1. Baseline characteristics of participants

Variables	Peri-articular injection	Intra-articular	p-value
Sex	M: 8 (32%), F: 17 (68%)	M: 7 (28%), F: 18 (72%)	0.29
Age	58.36±9.49	56.44±11.17	0.52
BMI ^a (Kg/m ²)	26.00±3.83	26.04±2.52	0.97
WOMAC ^b , Total Score, Points(SD ^c)	46.52±14.19	45.68±11.18	0.82
Pain	10.44±3.94	9.96±2.50	0.61
Stiffness	2.56±2.02	3.16±1.88	0.64
Function	33.88±10.10	32.60±8.05	0.35
VAS ^d	7.32±1.46	7.80±1.70	0.29
OKS ^e	23.52±7.77	24.72±7.13	0.58

a: BMI, body mass index; b: WOMAC, Western Ontario McMaster University Osteoarthritis Index (0-96); c: SD, Standard deviation; d: VAS, Visual Analogue Scale (0-10); e: OKS, Oxford Knee Scale (0-48)

Table 2. Comparison of VAS and OKS in both groups

Scale		Peri-articular	Intra articular	p-value (Within Groups)	p-value (Between Groups)
VSA ^a	Baseline	7.32±1.46	7.80±1.70	< 0.001	0.15
	4 th week	5.48±1.91	6.40±2.17		
	8 th week	5.00±2.27	5.90±2.69		
OKS ^b	Baseline	23.52±7.77	24.72±7.13	< 0.001	0.84
	4 th week	27.44±8.98	25.52±8.51		
	8 th week	28.36±9.62	27.76±8.67		

a: VAS, Visual Analogue Scale (0-10); b: OKS, Oxford Knee Scale (0-48)

Table 3. Comparison of WOMAC and subscales between the two groups

Variables		Peri-articular	Intra-articular	p-value (within groups)	p-value (between groups)
WOMAC ^a , Total (SD ^b)	Baseline	46.52±14.19	45.68±11.18	< 0.001	0.68
	4 th week	38.60±16.2	41.16±13.66		
	8 th week	36.44±16.2	39.36±14.88		
Pain	Baseline	10.44±3.94	9.96±2.50	< 0.001	0.65
	4 th week	8.36±4.23	8.84±2.95		
	8 th week	7.92±5.25	9.36±6.36		
Stiffness	Baseline	2.56±2.02	3.16±1.80	< 0.001	0.75
	4 th week	1.88±1.61	2.80±1.80		
	8 th week	1.84±1.54	3.20±2.70		
Function	Baseline	33.88±10.10	32.60±8.05	< 0.001	0.96
	4 th week	28.36±11.07	29.68±9.72		
	8 th week	26.68±11.19	26.96±11.47		

^aWOMAC, western Ontario McMaster University Osteoarthritis Index (0-96)

^bSD, standard deviation

4. Discussion

There is a favorable tendency in using prolotherapy as an alternative treatment for many musculoskeletal disorders. Several surveys have been done on the management of KOA with hypertonic dextrose injection. Recent studies emphasize the regenerating and healing aspects of dextrose prolotherapy (19-21). Also, there is some evidence of improvement in radiological grades in the long-term after prolotherapy and increasing in the articular cartilage thickness (22). Our study defined prolotherapy, either peri- or intra-articular injection, which caused a decrement in the WOMAC score (10.08, 6.32, respectively). Rabago and Patterson found a similar outcome in which dextrose injection resulted in meaningful improvement in the WOMAC composite score, 15.32 points at 52 weeks (23). Eslamian and Amouzande revealed that intra-articular dextrose injection created more decrement (30.5 points) in the WOMAC score (24). The reason could be due to the number of injections. We designed a double-set dextrose injection with two weeks' interval versus three sessions monthly, which were performed by other researchers, although occasionally more injections were needed (up to five sets) (23). Similarly, we used the VAS score to evaluate the effectiveness of prolotherapy in which there were no differences between the two groups in decreasing pain (2.32, 1.9, respectively, peri- and intra-articular injections ($p < 0.001$), which were consistent with other studies (25, 26). Furthermore, we completed the OKS questionnaire, which consists of important functional points (amount of the time able to walk without pain, limping or giving way the knee, etc.), which showed the same consequence (4.84 points peri-articular group, 3.04 points intra-articular group ($p < 0.001$)). We found that peri-articular injection with an easy procedure had been as effective as an intra-articular injection. An important point is that, by using a peri-articular approach, we avoid some probable serious side effects in critical patients; however, in our trial there were no significant complications. We performed a simple method in peri-articular injection, as described earlier. It could be as a replacement for the conventional approach (peppering protocol), which is a painful procedure causing the patients to use analgesia for few days. In our study, patients did not report any post-injection pain; it might be due to fewer insertions of the needle. This study revealed that prolotherapy could be a safe and effective administration in patients with knee osteoarthritis by moderate grades.

5. Conclusions

According to this study, we can conclude that a dextrose injection, either intra- or peri-articular, is an appropriate treatment for the knee osteoarthritis if the patients are selected correctly. It could be an inexpensive choice as well as an outpatient treatment compared with other management. We recommend performing more studies with larger sample size to support our findings. Using larger subjects could be more effective in the comparison evaluation and also better defining the probable side effects.

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Conflict of Interest:

There is no conflict of interest to be declared.

Authors' contributions:

Both authors contributed to this project and article equally. Both authors read and approved the final manuscript.

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