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Original Article

Effects of intra-articular versus peri-articular dextrose prolotherapy in knee osteoarthritis: A clinical trial study

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ABSTRACT

Objectives: This study aims to compare the effectiveness of intra-articular and peri-articular dextrose prolotherapy (DPT) in patients with knee osteoarthritis (KOA) without effusion.

Patients and methods: Between August 2018 and November 2018, a total of 51 participants including 27 cases (12 males, 15 females; mean age: 55.7±5.2 years; range, 38 to 70 years) in Group A and 24 cases (9 males, 15 females; mean age: 54.7±4.6 years; range, 38 to 70 years) in Group B were recruited. Group A received intra-articular DPT, while Group B received peri-articular DPT. Treatment was administered two times with two-week intervals. The Visual Analog Scale (VAS), Western Ontario and McMaster Universities Arthritis Index (WOMAC) and Oxford Knee Scale (OKS) questionnaires were filled at baseline, and four and eight weeks after first injection.

Results: At four and eight weeks, the VAS, OKS, and WOMAC scores improved from baseline in both groups. There was no significant difference in the WOMAC and OKS scores between two methods. The VAS scores showed superiority of intra-articular method ($p<0.05$).

Conclusion: Both peri-articular and intra-articular DPT were effective in patients with KOA. There was no superiority in terms of functional improvement between two groups. However, intra-articular prolotherapy was more effective in decreasing pain in these patients.

Keywords: Intra-articular injection, knee, osteoarthritis, prolotherapy.

Knee osteoarthritis (KOA) is a destructive and disabling disease which influences up to 6% of population more than 30 years old resulting in pain, joint stiffness and decreased function.[1] It affects most adults with age 65 or more with a prevalence of 33.6% (12.4 million) in the United States by the year 2008.[2] The origins of the pain are clearly unknown. However, it is believed that intra- and peri-articular structures are the sources of the pain.[2-4] There are several treatment options for KOA, ranging from pain killers to injection and surgery.[1,2] Prolotherapy is one of the injection-based therapies for KOA. It involves the injection of irritants like hypertonic dextrose for treatment of chronic musculoskeletal pain through the probable mechanism of proliferation of fibroblasts, collagen synthesis, and tissue healing.[5,6] The definite mechanism of action for dextrose prolotherapy (DPT) is unclear. However, several multimodal mechanisms have been suggested such as initiating a local inflammatory cascade inducing the growth factor and collagen deposition resulting in a connective tissue repair, strengthening of the structures and reducing pain.[7,8] Wilson et al.[9] also showed a multifactorial mechanism for DPT in this way that it dehydrated cells at the site of injection inducing cell rupture by producing an osmotic gradient which initiated an acute inflammatory cascade, followed by tissue healing. Several human studies have revealed the positive effects of DPT for different musculoskeletal disorders such as rotator cuff related shoulder pain

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and hallux rigidus.[6,10] There are favorable results for this method in KOA, as well.[5] Topol et al.[11] showed the chondrogenic effects of intra-articular DPT in severe KOA. Some other studies have shown that prolotherapy improves the pain, stiffness, physical function and flexion range of motion of the affected knee.[12-14] Pain of prolotherapy, as an its complication, is self-limited and usually subsides by painkillers such as acetaminophen. If the pain does not respond to acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and opioids are indicated.[15]

There are two main approaches to prolotherapy which are widely used, and physicians usually combine the aspects of both techniques. The first technique was called Hackett method. In this method, dextrose is the preferred irritant, with a frequency of treatment lasting months with sessions every 6 to 12 weeks. The West Coast method predominantly utilizes a combination of phenol, dextrose, and glycerin or sodium morrhuate with weekly sessions. In general, the injection of a small volume of an irritant solution on painful structures in several sessions every 2 to 12 weeks is the base of this method.[7] Since there are multimodal approaches for prolotherapy injection in KOA, and there are some concerns about the complications of the intra-articular injections such as septic arthritis that may cause to refuse the injection by the patients.[16] In addition, there are not enough studies to compare the efficacy and safety of peri-articular and intra-articular approaches for DPT in such patients. In the present study, we aimed to compare the effectiveness of these two methods on decreasing pain and improving functions in patients with KOA without effusion.

PATIENTS AND METHODS

Study design and study population

This single-center, double-blind, parallel-group, randomized clinical study was conducted at Shiraz University of Medical Sciences, Department of Physical Medicine and Rehabilitation (PMR) between August 2018 and November 2018. We allocated patients with KOA in a parallel group comparing the effects of intra-articular versus peri-articular DPT. The eligibility criteria included male and female patients with KOA without knee joint effusion who had knee pain, crepitation, and joint stiffness lasting for at least three months before the enrollment. Inclusion criteria were as follows: age between 40 and 70 years with a diagnosis of KOA based on clinical criteria of the American College of Rheumatology (ACR)[17] and negative ballottement test on physical examination and Grade 2 and 3 KOA based on Kellgren-Lawrence Grading Scale[18] that their clinical symptoms and signs lasted for at least three months before the enrollment. Exclusion criteria included patients with severe genu valgum or genu varum, active infection involving the knee or skin such as cellulitis, development of effusion during study, having history of intra- or peri-articular injection during the three last months, history of rheumatic or inflammatory disease involving the knee joints, prior total knee arthroplasty, poorly controlled diabetes mellitus with glycated hemoglobin (HbA1c) more than 7.5%, body mass index (BMI) more than 40 kg/m^2, history of knee trauma or fracture during the three last months, history of acute lumbosacral radiculopathy or peripheral neuropathy in both lower limbs, history of cancer, bleeding disorders, and pregnancy.

Randomization and blinding

In this study, a total of 60 participants were assessed for eligibility and included in the study. They were allocated to two parallel groups including intra-articular and peri-articular prolotherapy using blocked randomization assignment method and random block size of six. Out of 60, nine participants did not finish the study due to poor compliance and personal etiologies (n=3 in the intra-articular group and n=6 in the peri-articular group). Finally, 27 cases (12 males, 15 females; mean age: 55.7±5.2 years; range, 38 to 70 years) participated in Group A and other 24 cases (9 males, 15 females; mean age: 54.7±4.6 years; range, 38 to 70 years) participated in Group B.

For blinding, the patients were blinded to the group allocation. Considering two points of injection in peri-articular group in contrast to the only one point of injection in intra-articular group, the injector was recommended to insert the needle subcutaneously at the other point around the involved knee without injecting solution in the intra-articular group to improve patient's blinding. In addition, the researchers who followed the patients by questionnaires as well as statisticians were kept blind to the treatment allocation.

Interventions

Participation in this study was voluntarily. All patients were given a complete explanation about the study. They were assured they could withdraw from the study anytime they were not willing to continue study and this would not affect their treatment. At the

beginning of the study, demographic characteristics of participants were recorded including: sex, height, and weight. Before injections, the Visual Analog Scale (VAS), Western Ontario and McMaster Universities Arthritis Index (WOMAC), and Oxford Knee Scale (OKS) questionnaires were filled by participants. Then, injections were performed for both groups. The injection repeated two weeks later based on the allocated group technique. In Group A (intra-articular group), participants laid on bed with placing a pillow under the involved knee resulting in its flexion to 30 degrees and, then, the practitioner prepared the knee under sterile condition and marked the inferolateral side of the knee joint. Then, 5 mL of dextrose 25% by a 23-gauge syringe was injected at that site. Preparation of dextrose 25% included 2.5 mL of lidocaine 2% plus 2.5 mL of dextrose 50%. The final concentration of the solution was derived from the previous studies.[6,10] The injector also inserted the needle subcutaneously at the other point around the involved knee without injecting any solution in this group to improve patient's blinding. In Group B (peri-articular group), participants were placed in a supine position with the 30-degree knee flexion. The knee was examined and tender points were marked around the knee up to two points to puncture the skin. Then, 5 mL of dextrose 25% were injected under sterile condition by using a 25-gauge syringe around knee joint maximum in two points (lateral or medial) with almost 2.5 mL of solution injection for each point in different directions and subcutaneously using skin sliding. These points were the most painful points, except pes anserine bursitis. Preparation of dextrose 25% included 2.5 mL of lidocaine 2% plus 2.5 mL of dextrose 50%. For both groups, the second injection was performed two weeks after the first one. Prespecified protocols were achieved from a study by Farpour et al.[16] Both groups were asked to hold ice pack for 5 min on the puncture sites for first two days, have relative knee rest for 72 h, continue doing quadriceps isometric contraction exercises before injections.[19] The participants in both groups were asked to avoid consumption of anti-inflammatory medicine or other treatments for KOA. Then, they were asked to return two and six weeks after second injection (Weeks 4 and 8 after the first injection, respectively). During these visits, VAS, WOMAC, and OKS questionnaires were filled by the participants. In addition, we included one knee in participants with bilateral KOA which met the inclusion and exclusion criteria and, if both of knees were the same, we chose the right knee for this study.

Study outcomes

Demographic characteristics of participants were included age, sex, and radiological grading of the KOA. The VAS questionnaire with 0-10 scales used to assess severity of pain, in which 0 means without pain and 10 means the worst possible pain. The WOMAC which determined the patient's function, pain and stiffness was used. The questionnaire included three domains, pain (5 items), stiffness (2 items), and physical function (17 items). The validity and reliability of the Persian format of this questionnaire were confirmed previously.[20] The OKS was also used to assess patient's function consisting of 12 questions with 0-5 ordinal scale. The Persian version of this questionnaire was also valid and reliable.[21] For interpreting both WOMAC and OKS, each answer had five ordinal scales: none=0, mild=1, moderate=2, severe=3, extreme=4. The patients were followed by a second colleague who was not aware of the group allocation at baseline, four, and eight weeks after the first injections. The patients were also asked to mention any reaction and side effect.

Statistical analysis

Based on the previous study by Farpour et al.[16] and considering type one error of 5% (α=5%), power of 80% (effect size: 0.8), and β=0.2, the sample size was calculated 25 participants in each group. Statistical analysis was performed using the SPSS version 11.0 (SPSS Inc., Chicago, IL, USA) software. Continuous data were expressed in mean ± standard deviation (SD) or median (min-max), while categorical data were expressed in number and frequency. To analyze inter-group comparisons, repeated measure analysis of variance (ANOVA) and standard t-test were used. The paired t-test was used for intra-group comparison. A p value of <0.05 was considered statistically significant.

RESULTS

The baseline characteristics of participants, including age, sex, and the grade of radiology, are shown in Table 1. There was no significant difference between two groups in terms of demographic characteristics (p=0.78, p=0.67, and p=0.74, respectively).

Table 2 shows the mean VAS, OKS, WOMAC scores of the participants at baseline, four, and eight weeks after first injection. There was no significant difference between the groups at baseline for the scores obtained from each questionnaire (p=0.364 for WOMAC, p=0.067 for OKS, and p=0.251 for VAS).

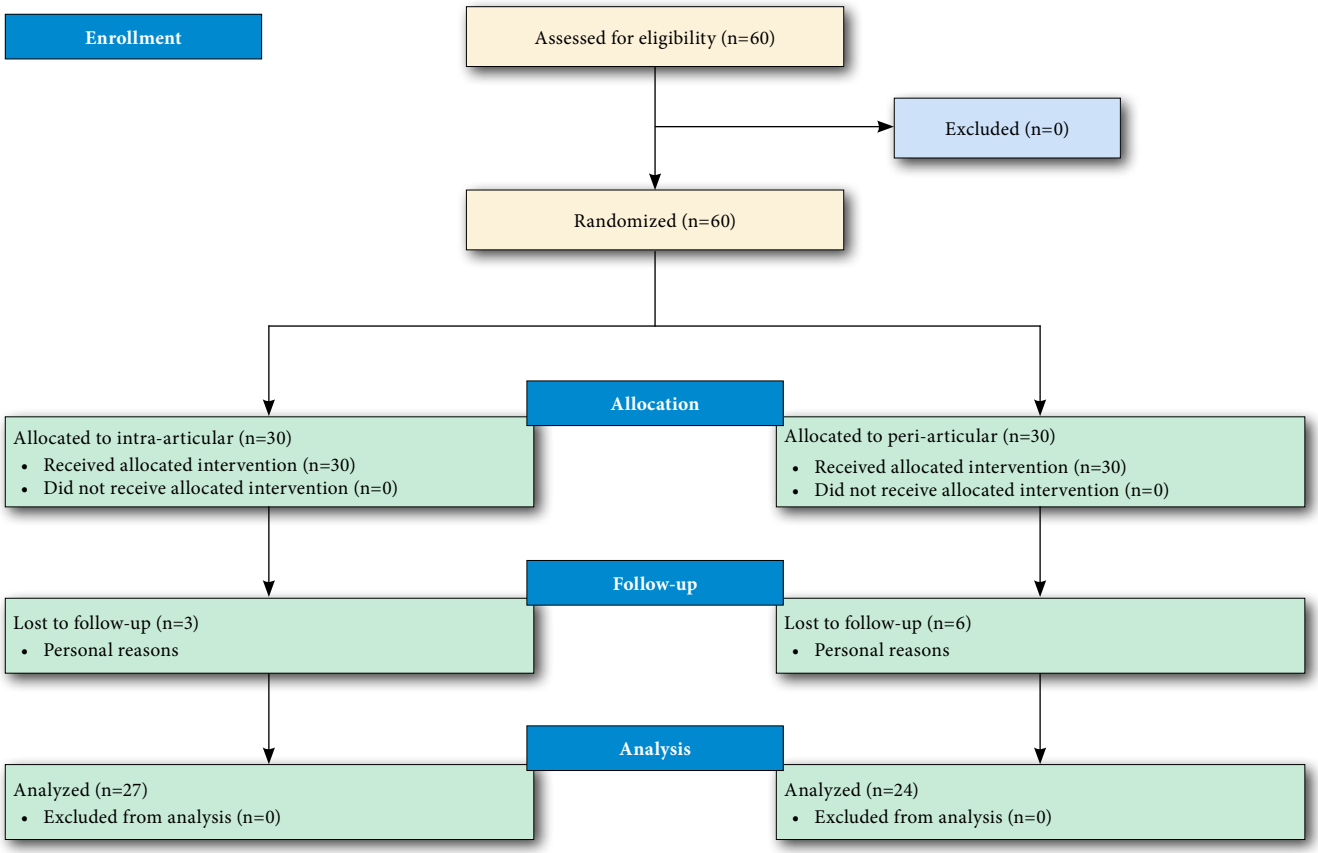

Figure 1. CONSORT flowchart.

The mean baseline WOMAC scores was 60.97±13.74 in the intra-articular group and 65.88±17.43 in the peri-articular group. After DPT, they improved through the fourth and eighth weeks (42.00±11.47, 31.60±11.30 in the intra-articular group and 43.92±13.37, 35.29±10.78 in the peri-articular group after four and eight weeks, respectively). The decrease in the mean WOMAC scores was significant within each group ($p<0.001$), but it was not significant between the groups ($p>0.05$).

Changes in the mean OKS scores also occurred in both groups throughout the study. Participants who underwent intra-articular prolotherapy had a mean OKS score of 34.00±3.33, 23.41±5.37, and 20.22±5.87 at baseline, four and eight weeks, respectively. In the other group who underwent peri-articular injection of 25% dextrose water (PASI-D25W), the mean OKS score was 32.25±4.05 at baseline, 23.59±5.16 at four weeks and 21.00±5.55 at eight weeks, respectively. The

TABLE 1
Baseline characteristics of intra-articular (Group A) and peri-articular (Group B) groups

	Group A			Group B			Between groups
Variables	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			55.7±5.2			54.7±4.6	0.67
Sex							0.78
Male	12	44.4		9	37.5		
Female	15	55.6		15	62.5		
Radiologic grade							0.74
Number of patients with Grade 2 knee osteoarthritis	22	81.5		18	75		
Number of patients with Grade 3 knee osteoarthritis	5	18.5		6	25		

SD: Standard deviation.

TABLE 2
Comparison of WOMAC, OKS and VAS scores between Intra-articular (Group A) and Peri-articular (Group B) prolotherapy groups in knee osteoarthritis

		Group A	Group B	Within groups	Between groups
Scale	Time	Mean±SD	Mean±SD	*p*	*p*
WOMAC	Baseline	60.97±13.74	65.88±17.43	-	0.364
	4th week	42.00±11.47	43.92±13.37	<0.001	0.449
	8th week	31.60±11.30	35.29±10.78	<0.001	0.179
OKS	Baseline	34.00±3.33	32.25±4.05	-	0.067
	4th week	23.41±5.37	28.59±5.16	<0.001	0.947
	8th week	20.22±5.87	21.00±5.55	<0.001	0.668
VAS	Baseline	7.52±1.01	7.92±1.06	-	0.251
	4th week	5.00±1.52	5.79±1.010	<0.01	0.032
	8th week	3.89±1.67	4.71±1.16	<0.001	0.040

WOMAC: Western Ontario and McMaster Universities arthritis index; OKS: Oxford Knee scale; SD: Standard deviation; VAS: Visual Analog Scale.

changes for OKS score were significant within each group (p<0.001), but they were not significant between the groups (p>0.05). The VAS scores decreased in both groups throughout the study. Based on the results, the mean VAS scores in the intra-articular group were 7.52±1.01, 5.00±1.52, and 3.89±1.67 at baseline, four, and eight weeks, respectively. The mean VAS scores in the peri-articular group were 7.92±1.06, 5.79±1.10, and 4.71±1.16 at baseline, four, and eight weeks, respectively. There was a significant improvement in the VAS scores within each group (p<0.01), as well as between two groups with a greater improvement in the

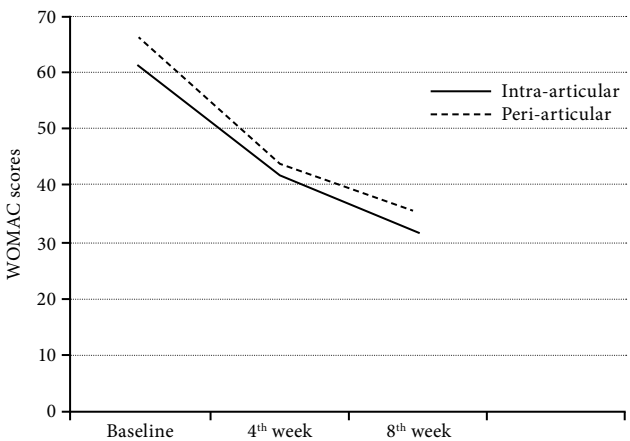

Figure 2. Trend of change in Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores in both intra-articular and peri-articular prolotherapy groups in patients with knee osteoarthritis.

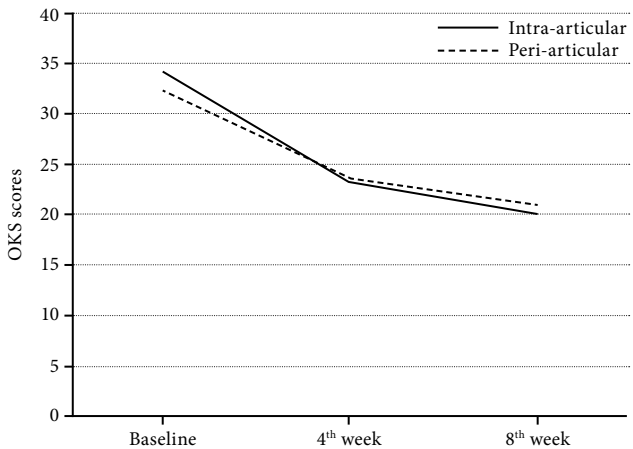

Figure 3. Trend of change in Oxford Knee scale (OKS) scores in both intra-articular and peri-articular prolotherapy groups in patients with knee osteoarthritis.

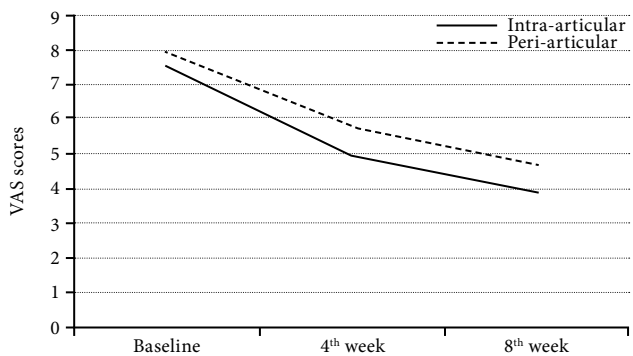

Figure 4. Trend of change in Visual Analog Scale (VAS) scores in both intra-articular and peri-articular prolotherapy groups in patients with knee osteoarthritis.

intra-articular group (p=0.032 at Week 4 and p=0.040 at Week 8 after injections). The trend of changes in WOMAC, OKS, and VAS scores is illustrated in Figures 2, 3 and 4, respectively.

DISCUSSION

Knee osteoarthritis is one of the most common debilitating diseases, particularly in elderly. Among a variety of treatment approaches, DPT is somewhat a novel approach in the management of many musculoskeletal disorders with the possible known mechanism of regeneration and tissue healing.[16,22] There are some evidences to show the improvement of radiological grades and ultrasonographic findings after prolotherapy in patients with tendon, ligaments or meniscal damages.[23] In addition, a study by Johnson et al.[24] revealed that DPT could directly induce the chondrocyte proliferation in patients with KOA when intra-articular approach was used. In the present study, we concluded that DPT with both peri-articular and intra-articular approaches were effective for decreasing pain and improving the function in participants with KOA at least for eight weeks after the injection with no superiority to each other in terms of improving function using WOMAC and OKS questionnaires. However, more pain reduction was achieved from the intra-articular prolotherapy approach by consideration of VAS scale. Farpour et al.[16] showed that there was no significant difference between two groups in terms of pain reduction and functional improvement in such patients using the same questionnaires. The results of the aforementioned study were somewhat similar to our study, particularly in terms of functional improvement using WOMAC and OKS questionnaires which could be due to the same sample size and injection methods. Having no significant difference between two groups in terms of functional status in such patients resulted from the aforementioned study and our study confirmed that peri-articular DPT could be an alternative technique for intra-articular method with the same efficacy in terms of functional improvement. However, we showed a greater pain reduction using the VAS scale in the intra-articular group that might be due to some differences between solution components, the volume of the injected solution, the number of injected points or the study group selection in this way that we excluded cases of KOA with joint effusion. Other study by Sit et al.[14] revealed that intra-articular DPT could decrease pain, improve function and quality of life in KOA, compared to blinded normal saline injections. The results are consistent with our study findings. However, it compared the effects of intra-articular DPT with placebo injection. Moreover, larger sample size, longer follow-ups, and the suprapatellar approach for intra-articular injection were the other differences between the aforementioned study and our study. Another study by Rezasoltani et al.[25] reported that peri-articular prolotherapy created more decreasing pain in contrast to intra-articular group using VAS scale in patients with KOA. The difference between the aforementioned study and our study can be attributed to the fact that their injection points corresponded to nerve exits and, therefore, they were lining up more with the concept of peri-neural injection treatment instead of peri-articular subcutaneous tender points performed in our study.

The difference between peri-articular subcutaneous prolotherapy and mesotherapy for the pain management is that mesotherapy is defined as an intradermal or subcutaneous analgesic injections mostly NSAIDs to increase the local concentration of them at the target site, as well as reducing their systemic side effects.[26] However, prolotherapy is a type of regenerative injection therapy using an irritant solution such as dextrose to induce inflammatory cascade and the release of cytokines with multifactorial mechanisms of actions resulting in proliferation of fibroblasts, collagen synthesis, and healing while injecting around or within the injured tissues.[5,6,16] In addition, more effectiveness of intra-articular DPT in our study might be due to the chondrogenic effects of this approach in patients with KOA according to some previous researches.[11,24]

Nonetheless, there are some limitations to our study. First, the sample size was calculated as 25. Although we selected 60 patients with KOA without effusion (30 in each group), nine participants (n=3 in the intra-articular group and n=6 in the peri-articular group) withdrew from the study and did not continue injection mainly due to poor attendance to follow-up visits (i.e., living in distant locations). Second, in this study, we included patients aged between 40 and 70 years, indicating a wide range of age. It may be more reasonable to narrow the age range of the participants. Third, despite no significant difference was observed between the two groups in terms of grade severity of KOA, and all patients had Grade 2-3 of severity, and it may be more appropriate to analyze the results for pain and function according to the radiological grade severity. In addition, we planned two injection sessions, but a previous study with more sessions showed different

results from our study. Thus, more injection sessions would be preferable. Furthermore, the follow-up period in our study was relatively short; therefore, further long-term studies are warranted. Moreover, the WOMAC questionnaire including patient's function, pain and stiffness should be analyzed separately to achieve more definite results about the efficacy of our interventions on each part. Finally, we followed patients by subjective assessments using mentioned questionnaires without evaluating the radiological changes after the injections. Lack of a placebo or control group was another limitations. Therefore, further multi-center, large-scale, long-term studies including control groups using objective assessment methods are recommended.

In conclusion, both peri-articular and intra-articular DPT had the same efficacy at least for a short period of time in patients with KOA. There was no superiority in terms of functional improvement between the two groups. However, intra-articular prolotherapy was more effective in decreasing pain in this patient population.

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Ethics Committee Approval: The study protocol was approved by the School of Medicine Shiraz University of Medical Sciences Ethics Committee (date: 22,05,2018, no: IR.SUMS.MED.REC.1397.088). The Iranian Registry of Clinical Trial (IRCT) approved this retrospectively registered study at 2018-07-18 with reference number "IRCT20171111037396N1". The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: All authors contributed equally to this article.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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REFERENCES

1. Samson DJ, Grant MD, Ratko TA, Bonnell CJ, Ziegler KM, Aronson N. Treatment of primary and secondary osteoarthritis of the knee. Evid Rep Technol Assess (Full Rep) 2007;157:1-157.
2. Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum 2008;58:26-35. doi: 10.1002/art.23176.
3. Yelin E. Cost of musculoskeletal diseases: Impact of work disability and functional decline. J Rheumatol Suppl 2003;68:8-11.
4. Felson DT. The sources of pain in knee osteoarthritis. Curr Opin Rheumatol 2005;17:624-8. doi: 10.1097/01.bor.0000172800.49120.97.
5. Zhao AT, Caballero CJ, Nguyen LT, Vienne HC, Lee C, Kaye AD. A comprehensive update of prolotherapy in the management of osteoarthritis of the knee. Orthop Rev (Pavia) 2022;14:33921. doi: 10.52965/001c.33921.
6. Nasiri A, Mohamadi Jahromi LS, Vafaei MA, Parvin R, Fakheri MS, Sadeghi S. Comparison of the effectiveness of ultrasound-guided prolotherapy in supraspinatus tendon with ultrasound-guided corticosteroid injection of subacromial subdeltoid bursa in rotator cuff-related shoulder pain: A clinical trial study. Adv Biomed Res 2021;10:12. doi: 10.4103/abr.abr_181_20.
7. Hsu C, Vu K, Borg-Stein J. Prolotherapy: A narrative review of mechanisms, techniques, and protocols, and evidence for common musculoskeletal conditions. Phys Med Rehabil Clin N Am 2023;34:165-80. doi: 10.1016/j.pmr.2022.08.011.
8. Bae G, Kim S, Lee S, Lee WY, Lim Y. Prolotherapy for the patients with chronic musculoskeletal pain: Systematic review and meta-analysis. Anesth Pain Med (Seoul) 2021;16:81-95. doi: 10.17085/apm.20078.
9. Wilson M, Topping A, Praet S. Current clinical considerations in the use of dextrose prolotherapy in sport and exercise medicine. Acta Scientific Orthopaedics 2022;5:7-16.
10. Hadianfard M, Safari B, Mohamadi Jahromi LS. Comparative effectiveness of the corticosteroid injection and prolotherapy in patients with hallux rigidus: A clinical trial. Iran Rehabil J 2023;21:127-34. doi: 10.32598/irj.21.1.1837.1.
11. Topol GA, Podesta LA, Reeves KD, Giraldo MM, Johnson LL, Grasso R, et al. Chondrogenic effect of intra-articular hypertonic-dextrose (prolotherapy) in severe knee osteoarthritis. PM R 2016;8:1072-82. doi: 10.1016/j.pmrj.2016.03.008.
12. Rabago D, Patterson JJ, Mundt M, Kijowski R, Grettie J, Segal NA, et al. Dextrose prolotherapy for knee osteoarthritis: A randomized controlled trial. Ann Fam Med 2013;11:229-37. doi: 10.1370/afm.1504.
13. Sert AT, Sen EI, Esmaeilzadeh S, Ozcan E. The effects of dextrose prolotherapy in symptomatic knee osteoarthritis: A randomized controlled study. J Altern Complement Med 2020;26:409-17. doi: 10.1089/acm.2019.0335.
14. Sit RWS, Wu RWK, Rabago D, Reeves KD, Chan DCC, Yip BHK, et al. Efficacy of intra-articular hypertonic dextrose (prolotherapy) for knee osteoarthritis: A randomized controlled trial. Ann Fam Med 2020;18:235-42. doi: 10.1370/afm.2520.
15. Rabago D, Slattengren A, Zgierska A. Prolotherapy in primary care practice. Prim Care 2010;37:65-80. doi: 10.1016/j.pop.2009.09.013.

16. Farpour HR, Fereydooni F. Comparative effectiveness of intra-articular prolotherapy versus peri-articular prolotherapy on pain reduction and improving function in patients with knee osteoarthritis: A randomized clinical trial. Electron Physician 2017;9:5663-9. doi: 10.19082/5663.
17. Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: An update with relevance for clinical practice. Lancet 2011;377:2115-26. doi: 10.1016/S0140-6736(11)60243-2.
18. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16:494-502. doi: 10.1136/ard.16.4.494.
19. Huang L, Guo B, Xu F, Zhao J. Effects of quadriceps functional exercise with isometric contraction in the treatment of knee osteoarthritis. Int J Rheum Dis 2018;21:952-9. doi: 10.1111/1756-185X.13082.
20. Bina E, Babaei-Ghazani A, Niknejad-Hosseyni SH, Toopchizadeh V, Sadeghi H. Reliability and validity of Persian version of Western Ontario and McMaster Universities Osteoarthritis index in knee osteoarthritis. J Anal Res Clin Med 2015;3:170-7.
21. Ebrahimzadeh MH, Makhmalbaf H, Birjandinejad A, Soltani-Moghaddas SH. Cross-cultural adaptation and validation of the Persian version of the Oxford knee score in patients with knee osteoarthritis. Iran J Med Sci 2014;39:529-35.
22. Heidari N, Ashraf A, Mohamadi Jahromi LS, Parvin R. Efficacy of perineural hypertonic saline injection versus acupoints of foot in the management of diabetic neuropathy: A multicenter, double-blinded randomized controlled trial. Pain Manag 2023;13:35-43. doi: 10.2217/pmt-2022-0042.
23. Fullerton BD. High-resolution ultrasound and magnetic resonance imaging to document tissue repair after prolotherapy: A report of 3 cases. Arch Phys Med Rehabil 2008;89:377-85. doi: 10.1016/j.apmr.2007.09.017.
24. Johnston E, Kou Y, Junge J, Chen L, Kochan A, Johnston M, et al. Hypertonic dextrose stimulates chondrogenic cells to deposit collagen and proliferate. Cartilage 2021;13(2_suppl):213S-24S. doi: 10.1177/19476035211014572.
25. Rezasoltani Z, Taheri M, Mofrad MK, Mohajerani SA. Periarticular dextrose prolotherapy instead of intra-articular injection for pain and functional improvement in knee osteoarthritis. J Pain Res 2017;10:1179-87. doi: 10.2147/JPR.S127633.
26. Paolucci T, Bellomo RG, Centra MA, Giannandrea N, Pezzi L, Saggini R. Mesotherapy in the treatment of musculoskeletal pain in rehabilitation: The state of the art. J Pain Res 2019;12:2391-401. doi: 10.2147/JPR.S209610.