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Comparison of the efficacy of ultrasound-guided dextrose 25% hypertonic prolotherapy and intra-articular normal saline injection on pain, functional limitation, and range of motion in patients with knee osteoarthritis; a randomized controlled trial

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Abstract

Background and aims Knee osteoarthritis (OA) is a debilitating condition that manifests as knee pain and dysfunction. Clinicians prefer non-surgical options such as intra-articular injections for mild to moderate disease. Dextrose prolotherapy (DPTx) has been shown to have a beneficial effect on knee OA in the long-term. In this randomized controlled trial (RCT), we aimed to compare DPTx with intra-articular normal saline injection (IA-NS) to treat knee OA in terms of effectiveness and patient-reported outcomes.

Methods The study was a double-blind RCT with an allocation ratio of 1:1. We used block randomization to assign patients to each treatment arm. Patients with a visual analog scale of at least 4 for pain, and a Kellgren–Lawrence scale of grade 2 or 3 (mild or moderate disease) were selected and assessed according to eligibility criteria. The participants received either 5 ml of 50% dextrose water or 5 ml of 0.9% sodium chloride. The patients were followed up at 2, 4, and 8 weeks. SPSS software was used for statistical analyses. All results were reported with a confidence interval of 95%, and a *p*-value of less than 0.05 was considered significant.

Results Overall, 55 patients were included in the study, but 50 completed the study process (25 patients in each treatment arm). The mean age of patients with knee OA was 62.98 ± 5.37, ranging from 55 to 74 years. We observed significant improvement in both groups in terms of knee pain, function, and knee extension degree at all follow-up visits ($p < 0.001$). Although DPTx was associated with better results than IA-NS, the difference was not statistically significant ($p > 0.05$). The adverse events were limited to injection-site pain and ecchymosis, which resolved by week 4.

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Conclusion Although we achieved slightly better results with DPTx, this treatment technique was not clinically or statistically superior to IA-NS in terms of knee pain and function in the short-term. Therefore, both DPTx and IA-NS are effective and well tolerated treatment options for knee OA. However, more RCTs are needed to confirm these claims.

Keywords Osteoarthritis, Knee, Prolotherapy, Dextrose, Intra-articular normal saline injection

Introduction

Knee osteoarthritis (OA) is a prevalent degenerative joint disease characterized by knee pain and dysfunction [1]. The release of inflammatory cytokines into the synovial fluid, and their detrimental effects on the articular cartilage and other components of joint tissue lead to the progression of OA [2, 3]. OA is more common in elderly women than in men, and its incidence is estimated to be 195 per 100,000 people [4, 5]. The risk factors include advancing age, female gender, traumatic joint injuries, obesity, physically demanding jobs, smoking, muscle weakness, sedentary lifestyle and decreased bone density [6].

Patients with knee OA are initially managed by administering conservative treatment options such as weight loss, physical and occupational therapy, aquatic therapy, acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and opioids. Minimally invasive procedures like intra-articular injections containing corticosteroids, hyaluronic acid (HA), platelet-rich plasma (PRP), and dextrose prolotherapy (DPTx) and genicular nerve block are other effective treatment options for mild to moderate knee OA. Surgery (e.g. total knee arthroplasty) is reserved for patients with severe knee OA, which is refractory to the previously mentioned non-surgical management [7–9].

DPTx is administered through several injection sessions, and is not associated with significant adverse events or complications [10, 11]. Several hypotheses have been proposed to explain the observed effect of DPTx; hyperosmolar dextrose creates an osmotic concentration gradient, which leads to necrosis, inflammation and subsequent tissue regeneration. Neurogenic inflammation, induction of autophagy or apoptosis are other proposed mechanisms [12]. A transient inflammatory response (i.e., a surge in CD43 + leukocytes and ED2 + macrophages) in animal models, and upregulation of MMP2, EGF, CXCL 9 and IL-22 in synovial fluid of patients with knee OA have already been described [13, 14].

This treatment modality has shown long-term benefits in treating intractable knee OA. However, there are few randomized controlled trials to assess its treatment outcomes and safety profile in comparison with intra-articular normal saline injection (IA-NS) [15, 16]. Moreover, a very limited number of studies have used ultrasound guidance to perform an accurate intra-articular knee injection, which is associated with better clinical outcomes and is more cost-effective than blind injections [17]. Thus, the current study was designed to directly compare the impact of dextrose prolotherapy (DPTx) on knee pain and function with that of intra-articular normal saline (IA-NS) injections in patients with knee OA.

Methods

Trial design and participants

This study is a double-blind randomized controlled trial (allocation ratio: 1:1). It was performed in a 6-month period from November 2022 to May 2023 on patients with chronic knee osteoarthritis referred to Emam Reza Clinic and Rajaee Hospital. Patients between 55 and 75 years of age with signs and symptoms of knee osteoarthritis, including knee pain, limitation of motion and joint stiffness for at least three months, with a visual analogue scale (VAS) of at least 4 for knee pain (according to the clinical criteria of the American College of Rheumatology) were recruited. Plain knee radiographs in anterior-posterior and lateral views were obtained for all patients, and those with a Kellgren–Lawrence scale (KLS) of grade 2 or 3 (i.e. mild or moderate disease) were retrieved for additional assessments. Patients with severe knee OA (KLS grade 4), peri-articular disease around the affected knee joint, knee infection, active lumbosacral radiculopathy, and a history of systemic conditions such as diabetes mellitus, systemic lupus erythematosus, rheumatic diseases, malignancies, and peripheral and central nervous system disorders were excluded. Additionally, patients on anticoagulants and those with a history of allergic reactions to the medications used in the study were not retained. Class III obesity with a body mass index (BMI) greater than 40, history of knee trauma, fractures, knee surgery, recent intra-articular injection (steroids in the last two months, and hyaluronic acid in the last 12 months), history of lower limb physical therapy within the last month, and severe lower limb deformity were other exclusion criteria. After completing the recruitment process based on the eligibility criteria, patients' previous medications, including NSAIDs and other analgesics were discontinued to avoid any interference with concomitant treatments. The study was approved by the Iranian registry of clinical trials (https://irct.behdasht.gov.ir), with the Clinical Trial Number IRCT20221111056470N1 on December 10th 2022.

Randomization, allocation, concealment, and blinding

Patients were randomly assigned to the dextrose prolotherapy or intra-articular normal saline injection

treatment group. The block randomization method was utilized for random allocation. Each block contained 4 samples, and Random Allocation software was used to generate a list of random numbers. For concealment, random sequencing was assigned to a person who was unaware of the research process, and questionnaires were completed by an individual who was uninformed about the group assignments. Furthermore, the participants, the care providers, and those assessing the outcomes were blinded after assignment to interventions. For this purpose, identical syringes and techniques (e.g. preparations, local anesthesia, ultrasound guidance, etc.) were utilized.

Interventions

In the intervention group, a mixture of 5 ml of 50% dextrose water and 5 ml of 2% lidocaine was prepared, and it was injected into the suprapatellar pouch. In the control group, a mixture of 5 ml of normal saline 0.9% sodium chloride and 5 ml of 2% lidocaine was administered in the control group. All the procedures were performed according to a sterile protocol. The injections were made in the suprapatellar pouch in a single ultrasound-guidance session using a 22-gauge sterile needle, while the patients were lying in the supine position with a pillow under the popliteal fossa to provide an optimal position for injection. The patients were instructed to use local ice for 10 min immediately after injection and 20 min three times a day for the next three days. The patients were taught to do specific home exercises including stretching exercises for hamstring, rectus femoris and calf muscles for at least 30 s, and isometric quadriceps exercises for 10 s. These exercises were administered three times a day with 10 repetitions. Potential side effects were pain at injection site, intra-articular or cutaneous infection, ecchymosis, bruising, hematoma formation, and drug-induced allergic reactions, which were assessed during follow-up visits.

Joint effusion was assessed via ultrasound using a Hitachi ARIETTA V60 (Hitachi Aloka Medical Systems, Tokyo, Japan) with a 5–18 MHz linear transducer. Patients were positioned supine with the knee flexed to 20° on a rolled towel. The transducer was first placed longitudinally on the patella and then moved proximally to visualize the suprapatellar recess. Effusion appeared as a hypoechoic or anechoic area between the prefemoral fat pad posteriorly and the quadriceps tendon, with the suprapatellar fat pad anteriorly. After identifying the suprapatellar recess, the transducer was rotated 90° and placed transversely along the distal quadriceps tendon at its patellar attachment. The needle was inserted laterally at the probe level and, under real-time ultrasound guidance using an in-plane technique, was advanced from lateral to medial toward the suprapatellar recess. All injections were delivered to patients by an experienced physical medicine and rehabilitation specialist (A.N.).

Outcomes

The primary outcome of this study were the total Western Ontario and McMaster Universities Arthritis (WOMAC) score and WOMAC subscales of pain, joint stiffness, and physical functional limitation [18]. Secondary outcomes were pain severity assessed with the VAS, and the Oxford Knee Scale (OKS) [19]. These questionnaires were administered just before the interventions, and at two, four and eight weeks after receiving the injection. Also, the degree of knee extension was measured during all follow-up visits to evaluate clinical performance improvement as a secondary outcome. All questionnaires have already been validated and verified in Persian [19–21]. The VAS is used for measuring pain severity from 0 to 10. A score of 0 means that the patient has no pain at all and a score of 10 means that the patient experiences the most severe pain. WOMAC score is comprised of three main subscales: pain, joint stiffness, and physical functional limitation, with five, two, and seventeen items in each subscale, respectively. Each item scores from 0 to 4 (0 as none, 1 as mild, 2 as moderate, 3 as severe, and 4 as extreme) with total score of 0 to 96. The OKS consists of twelve items that are used for assessment of function and performance. Each question scores from 0 to 4 (0 indicating the worst function, and 4 reflective of best function) with total score of 0 to 48.

Sample size and statistical analysis

The sample size calculation was based on the total WOMAC score and its subscales as the primary outcome. Data from two studies evaluating changes in the total WOMAC score and subscales from baseline to 8 weeks for the DPTx and IA-NS groups [22, 23] were extracted for power analysis. Considering a type I error (α) of 0.05, a power (1-β) of 0.80, and a probable drop-out rate of 30%, the maximum calculated sample size for each treatment arm was 13. Therefore, a total of 26 subjects were required for the final analysis. All the statistical analyses were performed using SPSS software version 25 (IBM Inc., Chicago, Illinois, USA). Data are presented as mean ± standard deviation (SD) and percentage (%) for frequency as appropriate. To assess the distribution of continuous numeric variables, we used the Kolmogorov-Smirnov (K-S) normality test. Base on K-S test results, independent t-test or Mann-Whitney u-test, and repeated measures test or Friedman test were used for comparison between the two groups, and within them, respectively. Absolute mean differences (MDs) between the groups at different time points were reported with 95% confidence intervals (95% CI). The significance level in all tests was less than 0.05 ($P < 0.05$).

Results

Overall, data from 87 patients were reviewed to assess eligibility. Of these 32 did not meet our criteria and were excluded for various reasons. In total, 55 patients were included in our study, and they were randomly assigned to two treatment arms of DPTx and IA-NS. During the follow-up, 2 of the 55 patients were unwilling to continue, 2 had poor compliance, and 1 experienced knee trauma. Thus, 50 participants met the criteria for the final analysis. The CONSORT flow diagram of this study is depicted in Fig. 1. The mean age of patients with knee OA was 62.98 ± 5.37, ranging from 55 to 74 years. Mean BMI was 28.05 ± 4.77, and ranged from 19.23 to 36.98. Women predominated and comprised 70% of the participants ($n = 35$). We found no significant difference in these demographic features between the two groups, as shown in Table 1.

There was a significant improvement in OKS and VAS within both treatment groups at 2, 4, and 8 weeks of follow-up ($p < 0.001$). In contrast, the comparison between the two groups in terms of OKS did not indicate a statistically significant difference at 2 weeks (MD = -0.84, 95%

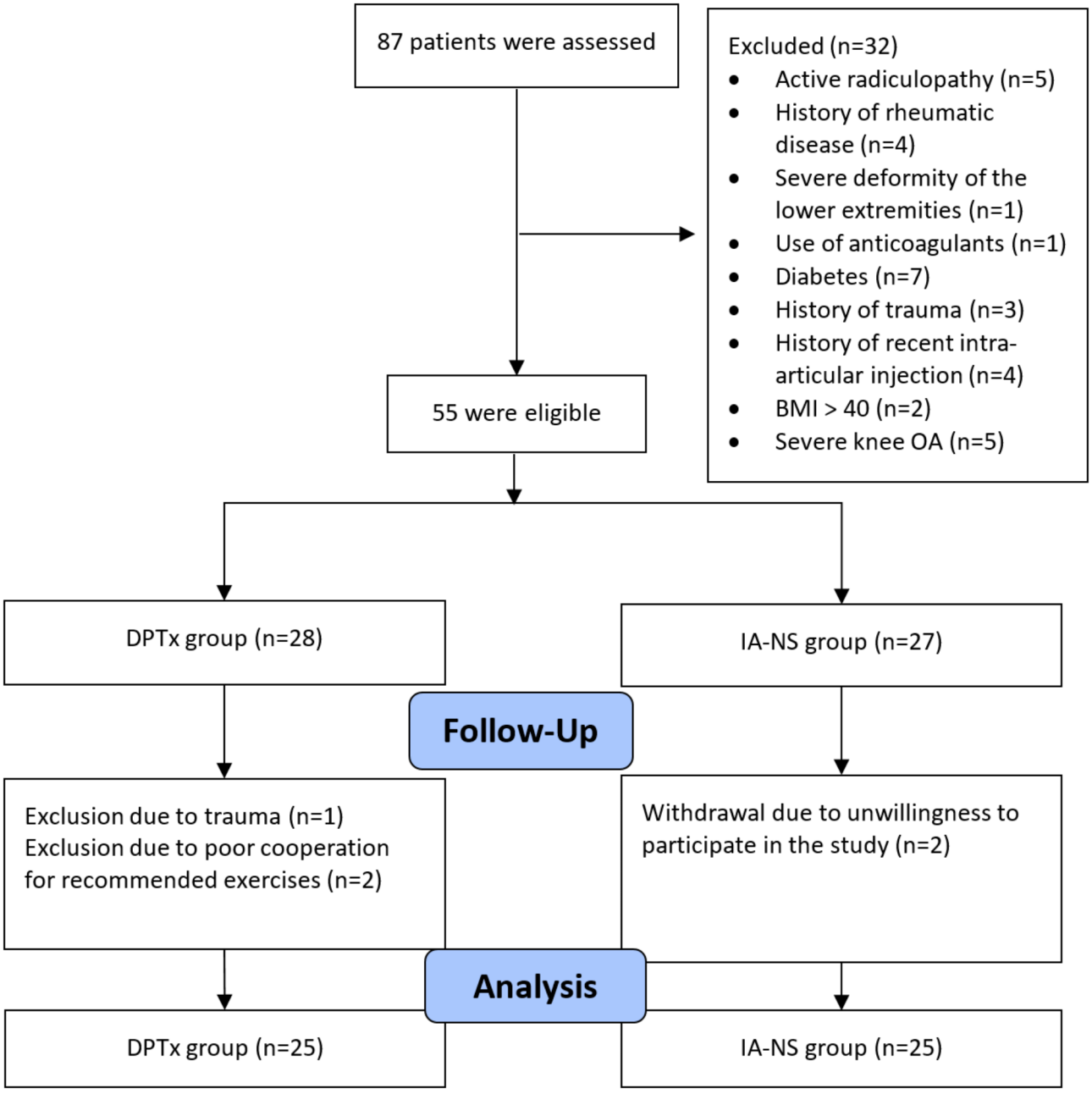

Fig. 1 CONSORT flow diagram of the study. BMI: body mass index; DPTx: dextrose prolotherapy; IA-NS: intra-articular normal saline injection

Table 1 Baseline demographic data and clinical features of the participants

Variable	Total; *n* = 50	DPTx; *n* = 25	IA-NS; *n* = 25	*P*-value
Age (years); mean ± SD	62.98 ± 5.37	63.24 ± 5.71	62.72 ± 5.12	0.736*
BMI (kg/m^2); mean ± SD	28.05 ± 4.77	28.35 ± 4.82	27.76 ± 4.79	0.665*
Weight (kg); mean ± SD	73.30 ± 10.75	74.28 ± 11.26	72.32 ± 10.34	0.525*
Height (cm); mean ± SD	162.08 ± 6.12	162.24 ± 5.97	161.92 ± 6.38	0.855*
Female Gender; n (%)	35 (70.0)	17 (68.0)	18 (72.0)	0.758**

SD: Standard deviation; DPTx: dextrose prolotherapy; IA-NS: intra-articular normal saline injection; BMI: body mass index

*Independent sample t-test, **Pearson Chi-square test

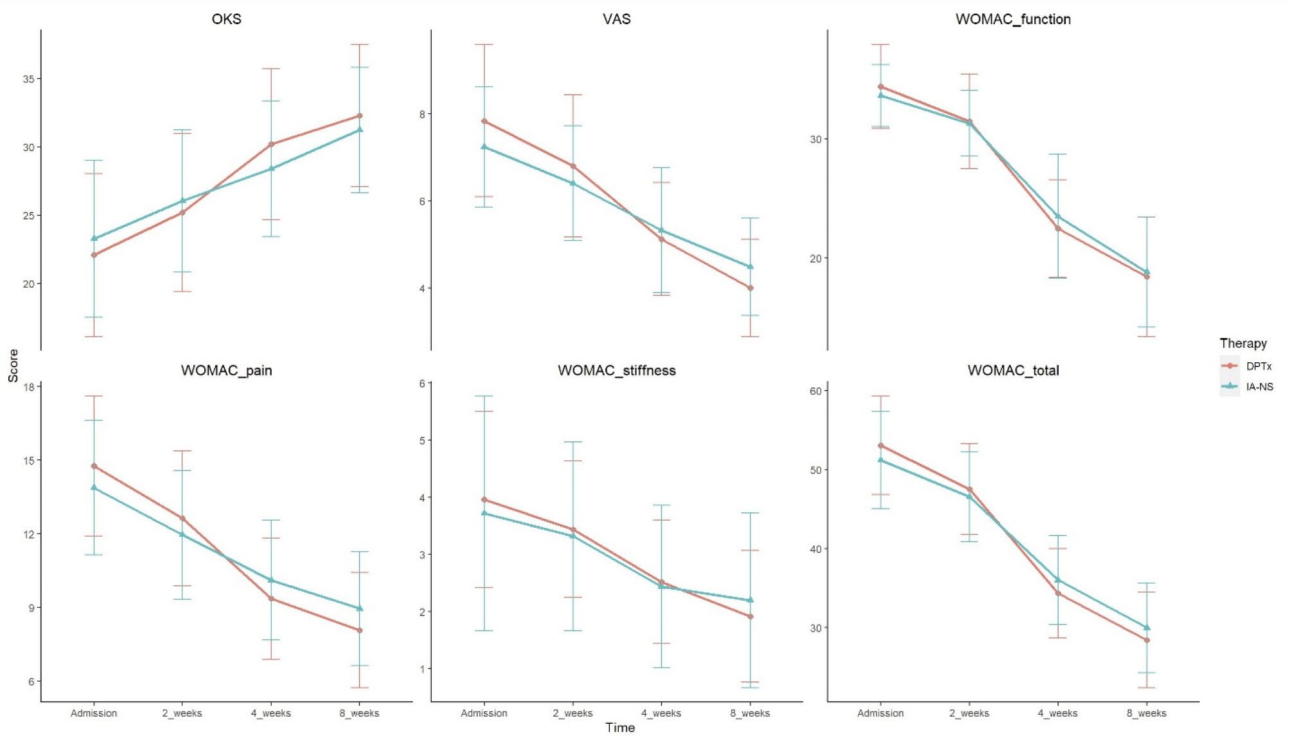

Fig. 2 Error bars of changes in OKS, VAS, and WOMAC score (subscales of pain, stiffness and function, and total score) in two treatment arms. DPTx: dextrose prolotherapy; IA-NS: intra-articular normal saline injection; OKS: Oxford Knee Score; VAS: Visual Analog Scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

CI: -3.89 to 2.21, $p = 0.59$), 4 weeks (MD = 1.8, 95% CI: -1.11 to 4.71, $p = 0.23$), and 8 weeks (MD = 1.04, 95% CI: -1.68, 3.76, $p = 0.46$) and for VAS at 2 weeks (MD = 0.40, 95% CI: -0.42 to 1.22, $p = 0.39$), 4 weeks (MD = -0.20, 95% CI: -0.96 to 0.56) and 8 weeks (MD = -0.48, 95% CI: -1.10 to 0.14, $p = 0.11$) during follow-up. Likewise, the total WOMAC score and its subsclaes of pain, stiffness, and function improved within both groups over time ($p < 0.001$). However, no significant difference in total WOMAC score was found between the two groups at 2 weeks (MD = 0.96, 95% CI: -2.22 to 4.14, $p = 0.56$), 4 weeks (MD = -1.68, 95% CI: -4.80 to 1.44, $p = 0.30$), and 8 weeks (MD = -1.56, 95% CI: -4.80 to 1.68, $p = 0.35$) during follow-up. Similarly, there were no significant differences between the two groups in the WOMAC subscales of pain, stiffness, and function at these time intervals ($p > 0.05$). Changes in OKS, VAS, and WOMAC scores over time are illustrated in Fig. 2.

To evaluate the clinical performance, knee extension degree was measured at all post-injection follow-up visits. In both groups, knee extension significantly improved ($p < 0.001$), which indicates the beneficial effects of both treatments, along with home-based exercises, in reducing knee flexion contracture in the short term. On the contrary, the knee extension degree did not differ between the two groups at 2 weeks (MD = -2.28, 95% CI: -5.83 to 1.27, $p = 0.21$), 4 weeks (MD = -1.28, 95% CI: -4.58 to 2.02, $p = 0.37$), and 8 weeks (MD = 2.12, 95% CI: -0.36 to 4.60, $p = 0.10$). A summary of the patient reported outcomes and their differences between the two groups is provided in Table 2.

There were no serious or major treatment-related adverse events such as infections, allergic reactions, or

Table 2 The comparison between DPTx and IA-NS groups in terms of changes in OKS and VAS, WOMAC score (subscales of pain, stiffness and physical function, and total score), and knee extension degree at admission, 2, 4 and 8 weeks after the intervention

Item	Group	Before intervention	2 Weeks	4 Weeks	8 Weeks	*P*-value within the group***
OKS	DPTx	22.08 ± 5.96	25.20 ± 5.79	30.20 ± 5.51	32.28 ± 5.20	< 0.001
	IA-NS	23.28 ± 5.75	26.04 ± 5.20	28.40 ± 4.97	31.24 ± 4.59	< 0.001
	MD (95%CI)	-	-0.84 [-3.89, 2.21]	1.80 [-1.11, 4.71]	1.04 [-1.68, 3.76]	-
	P-value between the groups*	0.472	0.592	0.231	0.457	-
VAS	DPTx	7.84 ± 1.75	6.80 ± 1.63	5.12 ± 1.30	4.00 ± 1.12	< 0.001
	IA-NS	7.24 ± 1.39	6.40 ± 1.32	5.32 ± 1.44	4.48 ± 1.12	< 0.001
	MD [95%CI]	-	0.40 [-0.42, 1.22]	-0.20 [-0.96, 0.56]	-0.48 [-1.10, 0.14]	
	P-value between the groups**	0.207	0.394	0.493	0.111	-
WOMAC Pain Score	DPTx	14.76 ± 2.85	12.64 ± 2.74	9.36 ± 2.46	8.08 ± 2.34	< 0.001
	IA-NS	13.88 ± 2.73	11.96 ± 2.62	10.12 ± 2.45	8.96 ± 2.32	< 0.001
	MD (95%CI)	-	0.68 [-0.81, 2.17]	-0.76 [-2.12, 0.60]	-0.88 [-2.17, 0.41]	-
	P-value between the groups	0.270*	0.353**	0.319**	0.188*	-
WOMAC Stiffness Score	DPTx	3.96 ± 1.54	3.44 ± 1.19	2.52 ± 1.08	1.92 ± 1.15	< 0.001
	IA-NS	3.72 ± 2.05	3.32 ± 1.65	2.44 ± 1.42	2.20 ± 1.53	< 0.001
	MD (95%CI)	-	0.12 [-0.68, 0.92]	0.08 [-0.62, 0.78]	-0.28 [-1.03, 0.47]	-
	P-value between the groups**	0.672	0.851	0.788	0.475	-
WOMAC Function Score	DPTx	34.36 ± 3.51	31.44 ± 3.96	22.48 ± 4.07	18.44 ± 4.99	< 0.001
	IA-NS	33.60 ± 2.61	31.28 ± 2.73	23.48 ± 5.19	18.84 ± 4.62	< 0.001
	MD (95%CI)	-	0.16 [-1.73, 2.05]	-1.00 [-3.59, 1.59]	-0.40 [-3.07, 2.27]	-
	P-value between the groups	0.236**	0.869*	0.452*	0.770*	-
WOMAC Total Score	DPTx	53.08 ± 6.24	47.52 ± 5.77	34.36 ± 5.64	28.44 ± 6.02	< 0.001
	IA-NS	51.20 ± 6.15	46.56 ± 5.71	36.04 ± 5.63	30.00 ± 5.68	< 0.001
	MD (95%CI)	-	0.96 [-2.22, 4.14]	-1.68 [-4.80, 1.44]	-1.56 [-4.80, 1.68]	-
	P-value between the groups*	0.289	0.557	0.297	0.351	-
Knee Extension Degree	DPTx	161.48 ± 7.01	165.00 ± 6.83	168.12 ± 6.18	174.24 ± 3.73	< 0.001
	IA-NS	164.36 ± 6.04	167.28 ± 5.93	169.40 ± 5.72	172.12 ± 5.10	< 0.001
	MD (95%CI)	-	-2.28 [-5.83, 1.27]	-1.28 [-4.58, 2.02]	2.12 [-0.36, 4.60]	-
	P-value between the groups	0.134**	0.210**	0.375**	0.100*	-

DPTx: dextrose prolotherapy; IA-NS: intra-articular normal saline injection; MD: mean difference; OKS: Oxford Knee Score; VAS: Visual Analog Scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; SD: Standard deviation

*Independent sample t-test, **Mann-Whitney U test, ***Friedman test

vasovagal reactions. Additionally, no complications led to study discontinuation. The only recorded adverse events were injection-site pain and ecchymosis in the second week of follow-up. The incidence of observed adverse events was almost identical in both groups. In DPTx group, 8 (32%) patients experienced injection-site pain, and 3 (12%) individuals had injection-site ecchymosis, while in the IA-NS group, these complications occurred in 7 (28%) and 4 (16%) patients, respectively. Neither of these adverse events persisted beyond the fourth week of follow-up.

Discussion

This clinical trial was conducted to evaluate the effectiveness of a single-session ultrasound-guided DPTx and IA-NS in patients with knee OA. A total of 55 patients meeting the eligibility criteria were randomly assigned to either treatment group. The results showed statistically significant improvements in clinical performance, function and pain intensity in both DPTx and IA-NS groups. However, there were no statistically significant differences between the two groups in terms of OKS, VAS, or WOMAC score at any time point, highlighting comparable outcomes between the treatments. The Patient

Acceptable Symptom State (PASS) for the WOMAC total score in knee OA patients ranges from 22.6 to 32.4 [24]. Based on this threshold, both treatment options were clinically effective at 8 weeks, with DPTx demonstrating a slight advantage (28.44 vs. 30). Transient injection-site pain and ecchymosis were observed in both groups, but no serious adverse events were noted.

The reduction in VAS and WOMAC scores, along with the enhancement in OKS and knee extension degree within both interventions is indicative of their effectiveness. These findings are corroborated by previous studies. For instance, in a study by Rabago et al. on patients with knee OA, both DPTx and IA-NS were effective in improving WOMAC scores. In contrast to our study, multiple injection sessions were administered, and the patients were followed up for a longer period, up to 52 weeks. They found that DPTx was superior to IA-NS in terms of pain and functional improvement in the long term [16]. Sit et al. compared DPTx and IA-NS in terms of efficacy after 52 weeks of injection. They also evaluated the WOMAC score, and concluded that DPTx was more effective than IA-NS in the long term [25]. Similarly, in another study by Farpour et al., intra-articular DPTx was shown to be effective in treating knee OA [26]. We also tracked the changes in the VAS, OKS, WOMAC score, and the knee extension degree in both treatment groups. Although the results at the 8th week were more satisfactory in DPTx group compared to IA-NS group, the observed differences were not statistically significant. This widening gap may herald the superiority of DPTx in the long term, as demonstrated at 52 weeks in previous studies [16, 25].

Intra-articular injection of hypertonic dextrose induces localized osmotic cellular stress, which will lead to cell disruption and subsequent tissue regeneration [12]. However, the overall effectiveness profile may be influenced by the innate properties of the procedure (e.g. injection site trauma and intra-articular volume expansion) [27]. The molecular mechanism through which the dextrose exerts its therapeutic effect remains equivocal. Nevertheless, several hypotheses have been proposed such as the following: A surge in inflammatory cytokines [13], the release of angiogenic and apoptotic factors [28], and chondrogenesis [29]. Analysis of synovial fluid in knee OA patients who received prolotherapy revealed upregulation of inflammatory cytokines, including MMP2, EGF, CXCL9, and IL-22, at 10 weeks [14]. In a study by Topol et al., DPTx resulted in prompt analgesia in grade IV knee OA along with alterations in neurocytokine levels that may mitigate pain; they observed an increase in substance P (SP) concentration at one week, and a reduction in neuropeptide Y (NPY) in three months [30]. In a study by Waluyo et al. on knee OA patients, urinary levels of C-terminal telopeptide of type-II collagen, a marker of cartilage breakdown in OA, were assessed. They found that its reduction following DPTx was more pronounced than with HA at three weeks [31].

Novel treatment approaches for knee OA are continuously being explored. A multicenter study demonstrated that a single HA injection effectively reduced pain and improved joint function in knee OA patients [32]. Additionally, intra-articular type-I collagen injection has shown to be beneficial with negligible side effects [33]. A review by Tarantino et al. highlighted high-intensity training as a promising therapeutic option for knee OA [34]. DPTx has been compared to other non-surgical treatment options for knee OA, and is considered a viable alternative. In a recent systematic review by Arias-Vázquez et al. which include 6 studies and 395 participants, DPTx was proposed as an alternative for HA injection with similar efficacy [35]. These findings align with those of Hashemi et al., who studied 100 patients and found DPTx to be as effective as HA injection in treating knee OA [36]. In another trial by Rahimzadeh et al. on 42 patients with knee OA, the effectiveness of DPTx was compared to that of PRP injection. Both techniques resulted in a reduced WOMAC score in 6 months, but PRP was slightly more effective [22]. In a more comprehensive study, Torani et al. compared DPTx effectiveness to that of erythropoietin, PRP, and radiofrequency prolotherapy in treating knee OA. In this study, erythropoietin was associated with better outcomes in comparison to other treatment approaches [37]. A recent meta-analysis comparing DPTx with PRP in terms of WOMAC scores found that DPTx was as effective as PRP on the pain subscale, but less effective on the stiffness subscale after six months [38].

We chose IA-NS for the control group, and found significant improvement in WOMAC subscales of pain and knee function in the short term, which is congruent with previous studies. A meta-analysis of the data from 1076 knee OA patients revealed that IA-NS as a placebo can improve patient-reported outcomes up to 6 months after the injection. This study suggested that IA-NS may have a true biological disease-modifying effect through the dilution of inflammatory mediators within the knee, and should not be used as a null control group [39]. The exact mechanism for this potential therapeutic effect is has not yet been identified. Therefore, the patients were informed that both treatment methods could improve symptoms, even if they were allocated to the control group (IA-NS). Our study is one of the few, particularly in the Iranian population, that compares DPTx efficacy with that of IA-NS to treat knee OA. We used ultrasound-guided injections, which are more accurate and result in better patient outcomes and compliance [17, 40]. The validated patient-reported outcome measures led to consistent and robust results. However, the current study had several

limitations. According to the results of a meta-analysis, IA-NS possesses a strong placebo effect, approaching the therapeutic range, particularly within 6 months [39]. Therefore, our control group was not entirely inert. The regenerative mechanisms induced by prolotherapy take several months (6–12 months) to result in healing, but the follow-up duration of our study was relatively short. There are no unanimous guidelines on the optimal number of prolotherapy sessions, as this depends on patient-specific factors. However, 2–6 sessions of DPTx at monthly intervals are generally recommended to achieve maximal therapeutic effect [10]. In the present study, we administered a single session of hypertonic dextrose, which may have impacted the results. We neither recorded nor compared disease severity according to KLS. It would have been useful to conduct other functional clinical tests, such as 6-minute walk test, 30-second chair stand test, timed up and go test, and stair climb test. We recommend additional multicenter trials with larger sample size and longer follow-up duration.

Conclusions

Single ultrasound-guided session of DPTx and IA-NS appear to be well-tolerated and effective treatment options in terms of reducing pain and improving WOMAC subscale of knee function in patients with knee OA. DPTx and IA-NS are clinically effective at 8 weeks, and are viable treatment options for knee OA in the short-term.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12891-025-08580-5.

Supplementary Material 1

Supplementary Material 2

Acknowledgements
None.

Author contributions
AN came up with the idea and conceptualized the study. AT wrote the initial draft and critically reviewed the manuscript. AT and NB analyzed the data and interpreted the results. AN and MSF were responsible for delivering the interventions. NB, MSF and AN collected the data. AN supervised the whole project, and MSF validated the results. All authors have read and approved the final version of the manuscript.

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Data availability
The data that support the findings of this study are available on request from the corresponding author (AN). The data are not publicly available due to ethical considerations.

Declarations

Human ethics and consent to participate
The protocol for this study was approved by the Medical Ethics Committee of Shiraz University of Medical Sciences with the reference number IR.SUMS.MED.REC.1401.246. The study was conducted in accordance with the Declaration of Helsinki. All participants completed written informed consent before entering the study. They were provided with information regarding the goals of the study, treatment methods, alternative choices, and their probable adverse reactions prior to enrollment. It was clarified that patients were able to leave the study at any time they desired.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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