*Phys Med Rehab & Electrodiagnosis* 2019; 1(4): 194-202
DOI: https://doi.org/10.22122/pmre.v1i4.48 **Published by** *Vesnu Publications*

*Original Article*

# Comparison of Efficacy between Dextrose Neurofascial Prolotherapy and Intra-articular Corticosteroid Injection in Patients with Moderate to Severe Knee Osteoarthritis: A Double-Blind Randomized Clinical Trial

Received: 27 July 2019
Accepted: 12 Oct. 2019
Published: 05 Dec. 2019

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**Keywords**
Prolotherapy; Injections; Intra-Articular; Osteoarthritis; Knee

**Abstract**

**Background:** Considering the large variety of medications prescribed in the treatment of knee osteoarthritis (OA) and uncertainty about their efficacy, the present study was conducted to compare the efficacy of dextrose neurofascial prolotherapy and intra-articular corticosteroid injection in patients with moderate to severe knee OA.

**Methods:** Qualified patients were randomly allocated to one of the two groups. The first group received one intra-articular injection of corticosteroid 40 mg plus 1cc lidocaine 1%. The second group received one intra-articular injection of 5 cc dextrose 20% through the lateral mid-patellar approach and four periarticular subcutaneous injections of dextrose 16% (4 cc dextrose 20% plus 1 cc lidocaine 1%) in 4 areas around the knee.

**Results:** The findings showed a significant improvement in all measured outcomes in steroid groups, but not in the function component and overall Western Ontario and McMaster Universities Arthritis Index (WOMAC) score of the prolotherapy group. No significant differences were observed between the groups in terms of the visual analog scale (VAS) and the WOMAC components of stiffness and function one month after treatment. In terms of the overall WOMAC score and pain component of WOMAC, the corticosteroid group showed significantly better results after one month (P = 0.046 and P = 0.007, respectively).

**Conclusion:** The results showed that both dextrose prolotherapy and corticosteroid intra-articular injection reduced pain and stiffness in patients with moderate to severe knee OA. In the short term, corticosteroid injection is superior to dextrose prolotherapy. To more precisely compare the effectiveness of these treatments in the long term, we recommend further studies with longer follow-up periods and larger sample sizes.

**How to cite this article:** Bayat M, Hadavand F. **Comparison of Efficacy between Dextrose Neurofascial Prolotherapy and Intra-articular Corticosteroid Injection in Patients with Moderate to Severe Knee Osteoarthritis: A Double-Blind Randomized Clinical Trial.** Phys Med Rehab & Electrodiagnosis 2019; 1(4): 194-202.



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## Introduction

The most common degenerative disorder leading to considerable economic burden on both patients and societies is knee osteoarthritis (OA). Knee joint degeneration occurs among one third of the population over 65 years old in the United States and causes joint pain, stiffness, and functional limitation.[1-3] Different conservative and surgical managements are considered for knee OA treatment; however, the surgical approach is reserved for severe refractory OA. Among conservative methods, including exercise, lifestyle modification, oral analgesics [non-steroidal anti-inflammatory drugs (NSAIDs)], laser therapy,[4] biofeedback,[5] and different intra-articular injections, prolotherapy is an alternative procedure categorized as regenerative medicine.[6]

Intra-articular injections are the most commonly applied non-surgical treatment options in this group of patients.[7,8] Corticosteroids are one of the most popular agents for intra-articular injection and are recommended by the American College of Rheumatology (ACR) practice guidelines for knee OA treatment. Other injection methods include hyaluronic acid,[9] Platelet Rich Plasma (PRP),[10] and ozone injection.[11] Although the short-term effectiveness of steroid injections has been shown in numerous studies, there are few documents about its long-term effects. Corticosteroid injection improves pain and function; however, it may cause cartilage damage and tissue atrophy. There are some concerns about the negative effects of long-term treatment through intra-articular steroid injections such as acceleration of joint destruction and cartilage damage.[12,13]

Among other injection methods, prolotherapy (growth factor or growth factor stimulation injection) is a not such a new treatment option. It has recently been studied more seriously and there is evidence to support its use.[14] It is a treatment method leading to the repair or functional restoration of soft tissue.[15] Soft tissue includes ligament, tendon, cartilage, and nerve. The injection increases growth factor levels promotes tissue repair or growth. The mechanism of action of prolotherapy may be through inflammatory or non-inflammatory mechanisms. Different solutions including dextrose, sodium morrhuate, phenol, platelet-rich plasma, and adult stem cells can be injected as a proliferative agent.[16] Among these agents, dextrose is one of the most commonly used. Simple dextrose and hyperosmolality and hypoosmolality exposure cause cells to proliferate and produce a number of growth factors.[17] The major strengths of this treatment method are its low cost and easy accessibility. The first description of prolotherapy was provided in a case report of temporomandibular joint (TMJ) injection in 1937. In 1950, the procedure was attempted in animal models.[18] Based on animal studies, the pain relief mechanism of prolotherapy is hypothesized to be through local healing stimulation of chronically damaged intra-articular and extra-articular components, increased joint stability by strengthening of injured ligaments, and cellular proliferation stimulation.[19] The effect of prolotherapy on chronic back pain and lateral epicondylitis was reported as inconclusive in a previous systematic review, while several randomized controlled trials (RCTs) on patients with refractory knee OA showed that those who underwent prolotherapy improved significantly over 30 months.[2,20,21]

There are 3 main methods of prolotherapy.[22] Enthesofascial intra-articular prolotherapy is the classic method. The injection location of this method is on the bony cortex or into the joints. Myofascial prolotherapy is the injection of specific soft tissue of the bony cortex, outside the joints, and under the subcutaneous fascia. The neurofascial prolotherapy approach involves an injection in the vicinity of the peripheral sensory nerves, and in particular, their physical penetration points reaching a subcutaneous plane.

Based on Hilton's law, the nerve that innervates the skin over a joint also innervates the joint and the muscles that move that joint.[23] Bennett found that sensory nerves are vulnerable to neuropraxia or axonal damage at

the point of skin penetration (chronic constriction injury).[24] This chronic injury causes inflammation leading to the discharge of some degenerative peptides such as calcitonin gene-related peptide (CGRP), substance P (SP), and nitric oxide (NO).[25,26] Peptides can be transported through the axon of sensory nerves in either direction, degenerative neuropeptides can move in an antegrade manner along the nerve to the spinal cord and then retrograde back to the joint and have degenerative effects. The result of neurofascial prolotherapy appears to be the restoration of function in these small sensory nerves.[16]

Although growth factors and other possible micro-substances leading to nerve repair are less well known, it seems that nerves respond to growth factors in a way similar to that of other tissue components. These observations have provided rationales for neurofascial prolotherapy.

A recent meta-analysis study showed that dextrose prolotherapy decreases pain symptoms and provides a better improvement than local anesthetics, exercise, and corticosteroids in OA patients.[27] Although prolotherapy has been used for treating musculoskeletal conditions for many years, the number of clinical trials assessing its efficacy in knee OA patients is still limited.[1,2,20-22]

Most of the nonsurgical treatment options mostly affect non-severe OA (grade two or three OA). In this study, the authors decided to enroll patients with grade 3 and 4 OA who -due to a medical condition or their refusal-were not a candidate for replacement surgery. Considering the large variety of medications prescribed in the treatment of knee OA and uncertainty about their efficacy, the present study was conducted to compare the efficacy of dextrose neurofascial prolotherapy and local corticosteroid injection in patients with moderate to severe knee OA.

## Methods

*Study population:* The present study was a double-blind, randomized, clinical trial. Patients aged 45 to 75 years who were diagnosed with knee OA and referred to Mahdiyeh Hospital, Tehran, Iran, affiliated with Shahid Beheshti University of Medical Sciences, Tehran, in 2016 were recruited in this trial. The study inclusion criteria included an approved diagnosis of knee OA based on the American College of Rheumatology (ACR) standard clinical criteria, conservative treatment (including medication and exercise) without improvement in the past 3 months, body mass index (BMI) of less than 35, and Kellgren-Lawrence (KL) grade 3 or 4 cartilage destruction based on weight-bearing knee radiographs. The exclusion criteria were history of knee intra-articular injections, arthroscopic or open surgeries in the past 3 months, history of recent severe knee trauma, septic arthritis of the knee, presence of an active ulcer in the injection site, genu varum or genu valgum of over 20 degrees, positive history of systemic diseases such as rheumatoid arthritis or diabetes, and allergy to the intended medications.

*Interventions:* In the present study, 38 eligible patients were randomly assigned to one of two groups. The first group received one intra-articular injection of triamcinolone 40 mg plus 1 cc lidocaine 1%. The injection was performed at the lateral mid-patellar region with the knee extended.

The second group received one intra-articular injection of 5 cc dextrose 20% through lateral mid-patellar approach and 4 periarticular subcutaneous injections of dextrose 16% (4 cc dextrose 20% plus 1 cc lidocaine 1%) in 4 areas around the knee (two areas in about 2 inches proximally and laterally of the proximal pole of the patella, one in the medial aspect of the joint line, and one in the midpoint between the tibial tuberosity and fibular head). These mentioned areas were approximate points of fascial penetration of sensory nerves to enter the subcutaneous tissue.[11] To make sure that the nerve has been effectively injected, the injections were accomplished in a circular pattern around the needle entrance site with about 5 points of infiltration of 1 cc of

solution (with 1 puncture of the skin). Figure 1 shows the periarticular injection points in the prolotherapy group. In subjects with a complaint of pain in the pes anserine area, 2 cc of dextrose 16% was also injected into the region.

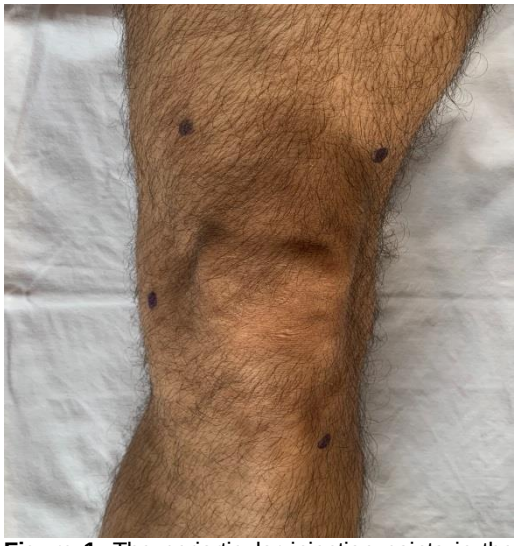

**Figure 1.** The periarticular injection points in the prolotherapy group

The 22 gauge sterile needle was used in both groups. After 15 minutes of rest following injection, patients actively performed knee extension and flexion to ensure suitable distribution of the solution. Patients were advised to rest and have limited weight bearing on the injected leg in the next 2 days. Cold compresses were recommended 3 times for 10 minutes on the day of injection. Patients were also advised to perform multi-angle isometric exercises of the knee 3 times a day.

*Data collection:* Patients were interviewed at baseline and 1 month after the procedure by a trained evaluator (blinded to the injection process) using a checklist for general information, the visual analog scale (VAS), and a validated Persian translation of the Western Ontario and McMaster Universities Arthritis Index (WOMAC) to evaluate pain and disability.

WOMAC includes 5 questions about pain, 2 questions on joint stiffness, and 17 about functional limitations. Each question is scored on a scale of 0 to 4 and the total score ranges from 0 to 96. The validity and reliability of the Farsi translation of WOMAC were evaluated and confirmed Eftekharsadat et al. in 2015.[28]

*Statistical analysis:* The continuous variables are presented as mean ± standard deviation (SD) and categorical variables as frequency and percentage. Chi-squared test, (Fisher's exact test if needed) were used to compare categorical variables. Student's t-test and analysis of variance (ANOVA) were used to compare the two groups in terms of means.

Data analysis was performed using SPSS software (version 22, IBM Corporation, Armonk, NY, USA), and P-values of less than 0.05 were considered statistically significant.

*Ethical considerations:* The study protocol adhered to the recommendations of the Declaration of Helsinki. All participants in this study signed an informed consent form. In addition, the study was reviewed and approved by the ethics committee of Shahid Beheshti University of Medical Sciences.

## Results

The study participants included 40 patients who were randomly assigned to the 2 groups (20 patients in each group). Figure 2 shows the sample selection process.

In each group, 1 patient was excluded from the analysis, and thus, data of 38 patients (19 in each group) were analyzed. The mean age of patients in the corticosteroid and prolotherapy groups was 61.05 ± 5.0 and 63.0 ± 7.46 years, respectively. Baseline characteristics of patients are presented in table 1, indicating no statistical difference between the two groups in terms of the variables.

The results of the follow-up evaluation of groups are presented in table 2. At the 1-month follow-up, the findings showed a significant improvement in all measured outcomes in the corticosteroid group. In the prolotherapy group, VAS, and the pain and stiffness component of WOMAC significantly improved, but this improvement was not observed in the function component and overall WOMAC score.

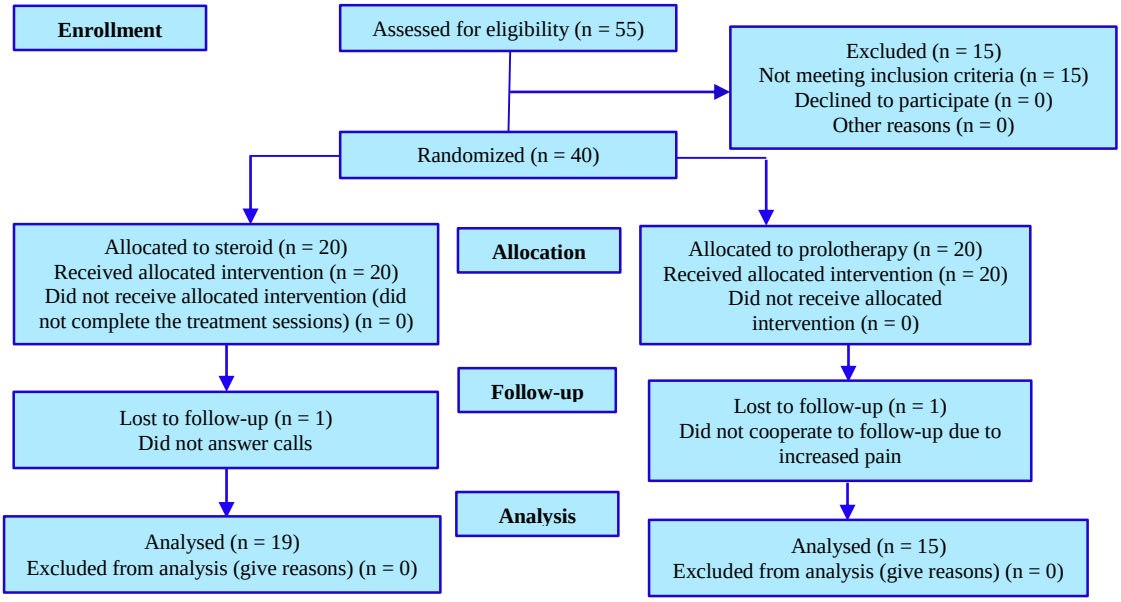


**Figure 2.** CONSORT flow diagram

The comparison of the two groups in the first month of follow-up showed that there were no significant differences between groups in terms of VAS and WOMAC components of stiffness and function (Table 3). Although the WOMAC pain component showed remarkable decrease in both groups, the findings showed significantly better results in the steroid group (P = 0.007). Based on the total WOMAC score, the corticosteroid group showed significantly more improvement (P = 0.046).

Considering VAS scores, after 1 month, both groups showed a significant decrease in pain (P < 0.0001 and P = 0.006 for corticosteroid and prolotherapy, respectively).

**Table 1.** General characteristics of patients

| Quantitative variables (mean ± SD) | Groups | | P |
|---|---|---|---|
| | Corticosteroid (n = 19) | Prolotherapy (n = 19) | |
| Age (years) | 61.05 ± 5.03 | 63.00 ± 7.46 | 0.35 |
| **Qualitative variables [n (%)]** | | | |
| Gender | | | 0.426 |
| Female | 16 (84.2) | 14 (73.7) | |
| Male | 3 (15.8) | 5 (26.3) | |
| Occupation | | | 0.180 |
| Housewife | 15 (78.9) | 17 (89.5) | |
| Nurse | 1 (5.3) | 0 (0.0) | |
| Retired | 1 (5.3) | 0 (0.0) | |
| Worker | 1 (5.3) | 0 (0.0) | |
| Employee | 1 (5.3) | 0 (0.0) | |
| Carpet weaver | 0 (0.0) | 1 (5.3) | |
| Driver | 0 (0.0) | 1 (5.3) | |
| Affected side | | | 0.113 |
| Right | 5 (26.3) | 9 (47.4) | |
| Left | 5 (26.3) | 4 (21.1) | |
| Both | 9 (47.4) | 6 (31.6) | |
| Grade | | | 0.937 |
| Two | 1 (5.3) | 1 (5.3) | |
| Three | 13 (68.4) | 12 (63.2) | |
| Four | 5 (26.3) | 6 (31.6) | |

**Table 2.** Intragroup outcome changes at 1-month follow-up

| Difference between measurements | | Corticosteroid (n = 19) | | Prolotherapy (n = 19) | |
|---|---|---|---|---|---|
| | | M diff (SD) | P | M diff (SD) | P |
| VAS scale | | 3.63 (2.00) | < 0.0001 | 2.78 (2.07) | < 0.0001 |
| WOMAC index | Pain | 4.57 (3.84) | < 0.0001 | 1.78 (2.50) | 0.006 |
| | Stiffness | 1.78 (1.93) | < 0.0001 | 0.89 (1.72) | 0.037 |
| | Function | 12.10 (11.44) | 0.001 | 0.47 (9.41) | 0.829 |
| | Overall | 19.57 (15.85) | < 0.0001 | 3.15 (11.35) | 0.241 |

M diff: Mean difference; SD: Standard deviation; VAS: Visual analogue scale; WOMAC: Western Ontario and McMaster Universities Arthritis Index

The mean difference of VAS index scores were 3.63 and 2.78 in the corticosteroid and prolotherapy groups, respectively. As shown in table 2, between group differences were not significant.

Both groups showed significant improvement in the WOMAC pain component. A greater pain reduction was observed in the corticosteroid group compared to the prolotherapy group. The mean difference scores of the WOMAC pain component were 4.57 and 1.78 in the corticosteroid and prolotherapy groups, respectively (Table 2).

The score of joint stiffness in both groups decreased significantly after 1 month. Mean difference scores of stiffness were 1.78 and 0.89 in the corticosteroid and prolotherapy groups, respectively. Although not significant, the corticosteroid group showed greater improvement.

The corticosteroid group showed a significant improvement in the function component of the WOMAC index in 1 month. In the prolotherapy group, the mean difference was very small and not significant (Table 3).

Considering the function component, there was no significant difference between the two groups.

## Discussion

Due to concerns about the negative effects of long-term treatment with intra-articular steroid injection[29] and searching for a more effective treatment in patients, the present study was conducted to compare the efficacy of dextrose neurofascial prolotherapy with corticosteroid.

Results of the present study showed that dextrose neurofascial prolotherapy can decrease pain in knee OA patients. The results of a systematic review conducted by Hassan et al. showed that prolotherapy can help achieve considerable symptomatic control in people with OA.[16]

In our study, the function component of WOMAC did not show significant improvement in the prolotherapy group. Our explanation for this finding is the short follow-up time of the present study.

**Table 3.** Between group outcome differences at baseline and 1-month follow-up

| Osteoarthritis status | | | Corticosteroid (n = 19) | Prolotherapy (n = 19) | P |
|---|---|---|---|---|---|
| | | | Mean ± SD | Mean ± SD | |
| VAS scale | | Before Rx | 7.57 ± 1.64 | 8.23 ± 1.61 | 0.222 |
| | | 1 month after Rx | 3.94 ± 2.83 | 5.44 ± 2.80 | 0.110 |
| WOMAC index | Pain | Before Rx | 10.05 ± 3.20 | 11.36 ± 3.38 | 0.227 |
| | | 1 month after Rx | 5.47 ± 5.25 | 9.57 ± 3.28 | 0.007 |
| | Stiffness | Before Rx | 3.42 ± 1.46 | 3.84 ± 2.47 | 0.528 |
| | | 1 month after Rx | 1.63 ± 2.00 | 2.94 ± 2.17 | 0.060 |
| | Function | Before Rx | 30.26 ± 10.82 | 26.68 ± 16.10 | 0427 |
| | | 1 month after Rx | 18.15 ± 15.01 | 26.21 ± 15.07 | 0.108 |
| | Overall | Before Rx | 44.73 ± 14.69 | 41.89 ± 20.18 | 0.352 |
| | | 1 month after Rx | 25.15 ± 21.58 | 38.73 ± 18.89 | 0.046 |

Rx: treatment; SD: Standard deviation; VAS: Visual analogue scale; WOMAC: Western Ontario and McMaster Universities Arthritis Index

Moreover, at the 1-month follow-up, corticosteroid showed superior pain reduction effects compared to prolotherapy. Previous studies have shown that corticosteroids can provide short-term pain relief in OA patients.[27,30-32] Dextrose prolotherapy requires more time to induce progressive improvement and clinical experience suggests that repeat and tune-up sessions improve outcomes after 52 weeks.[1] Many previous studies have not reported analysis on effect size, but Cohen's effect size calculations in some studies showed that prolotherapy can have a significant positive effect on WOMAC and pain subscale scores as soon as 12 weeks following treatment and this positive effect can continue for about 2.5 years after treatment.[4,33] Jahangiri et al. found that corticosteroid has better results after 1 month of treatment, but prolotherapy seemed to be more effective after 6 months.[34]

In the present study, the authors evaluated the effects of neurofascial combined with intra-articular dextrose prolotherapy. The mechanism of action of this method is explained extensively in the introduction of this article. As mentioned earlier, the main targets of injection in this method are peripheral sensory nerves at the point of their fascial penetration. It is hypothesized that sensory nerves are prone to chronic constriction injury (CCI) at this point and treating this injury can result in improvements in articular cartilage. Very few studies have evaluated neurofascial prolotherapy. In a study conducted by John Lyftogt in 2005, 127 painful knees, shoulders, and elbows were treated with subcutaneous prolotherapy.[35] The mean duration of symptoms and treatment in this study was 23.9 months and 7 weeks, respectively. The mean VAS initially decreased from 6.7 to 76.7% with a mean follow-up of 21.4 months. The patient satisfaction rate with follow-up was 91.7%. The treatment was well-tolerated and safe. In another study, Lyftogt focused on the treatment of Achilles tendons.[36] He treated more than 300 Achilles tendons with more than 90% success.[36] In a study similar to our trial, Rezasoltani et al. found that periarticular dextrose prolotherapy is as effective as intra-articular injections, and in some aspects, it even showed greater effectiveness.[37] Periarticular injections have also been successfully used in patients undergoing total knee arthroplasty.[38]

The major limitation of this study was the short follow-up duration. We guess that in longer follow-up durations, the results would be more in favor of prolotherapy. The other limitation was a relatively small sample size. Our measurement tools included VAS and WOMAC both of which are subjective and less reliable than objective measurement tools. Strength points included consistent results and few missing data. We recruited subjects with moderate to severe knee OA who were not candidates for surgery. Although the treatment response could be less significant, finding methods of decreasing pain and disability can be promising for this group of patients and delay the need for surgery.

## Conclusion

According to the findings of the present study, both dextrose prolotherapy and local corticosteroid injection can decrease pain and stiffness in patients with moderate to severe knee OA. Prolotherapy requires a longer time to improve function, and in the short term, corticosteroid injection is superior to dextrose prolotherapy.

To more precisely compare the effectiveness of these treatments, we recommend further studies with longer follow-up periods and larger sample sizes.

## Acknowledgments

None.

## Conflict of Interest

Authors have no conflict of interest.

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