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# Effectiveness of Prolotherapy Injection in Elderly Patients with Knee Osteoarthritis: A Double-Blind Randomized Controlled Trial

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## Abstract

**Background :** Knee osteoarthritis (OA) is a painful chronic disease in elderly population. Research has shown that prolotherapy is an effective pain-relieving treatment, particularly when used in combination with other therapies. The aims of this study was to evaluate the effectiveness of prolotherapy for knee OA based on The Western Ontario McMaster University OA Index (WOMAC) composite score (100 points), Knee Pain Scale, and self-reported satisfaction. We performed a randomized-controlled trial (RCT) with a double-blinded approach.

**Methods :** An injection saline, 10% dextrose (D10) prolotherapy, or at-home knee exercise was administered to twenty-seven elderly patients (≥60 years old) experiencing painful knee OA for at least three months. Extra- and intra-articular injections were administered at weeks 1, 4, and 7, with follow-up at weeks 11 and 15. Exercise group received in-person training and an exercise guidebook. WOMAC composite score (100 points), Knee Pain Scale, and self-reported satisfaction evaluated the outcomes. The results were considered statistically significant if $p < 0.05$.

**Results :** There are no significant difference in baseline among groups. At 21 weeks, all groups exhibited improved composite WOMAC scores ($p$ <0.02) compared to baseline. After adjusting for age, sex, and body mass index, D10 prolotherapy showed a significant WOMAC score improvement at 21 weeks ($p$ <0.04) compared to saline and exercise (score change: 16.2 ± 4.4 vs. 8.5 ± 4.3, and 9.1 ± 3.2, respectively), surpassing the minimal clinically significant difference based on WOMAC. Self-reported satisfaction with D10 prolotherapy was high without reported adverse effects.

**Conclusion :** When compared to saline injections and at-home exercises, D10 prolotherapy resulted in a clinically significant sustained improvement in pain, function, and stiffness scores for knee OA in elderly.

**Keywords :** dextrose, knee, pain, prolotherapy, osteoarthritis.

## INTRODUCTION

Osteoarthritis (OA) of the knee is a chronic condition that causes stiffness, discomfort, and functional loss of joints.[1] By 60, radiographic evidence of OA is present in most elderly.[2] Pain can originate from intra-articular structures within the joint and supportive extra-articular structures surrounding it.[3] Although multidisciplinary care is the standard, a recent comprehensive study found no significant advantages to any particular therapy.[4] Oral vitamins and conservative treatment, such as pain-relieving medication, have been studied, although their effectiveness is unclear.[5]

Prolotherapy is an injection therapy used to treat persistent musculoskeletal injuries, such as knee osteoarthritis (OA).[6] Its fundamental idea involves administering tiny amounts of an "irritant" solution to several damaged ligament and tendon insertions and nearby joint areas for several treatment sessions.[7] According to current theories, prolotherapy promotes the inflammation-induced local repair of extra and intra-articular tissue damage.[8] One injectant that is frequently utilized is hypertonic dextrose. It targets several possible pain sources in and around the injured knee joint.[9]

Despite their methodological weaknesses, one open-label study and one randomized controlled trial (RCT) indicated improved outcomes in response to prolotherapy.[10,11] Therefore, we conducted a double-blind RCT to ascertain whether elderly patients with symptomatic knee OA receiving prolotherapy would experience a more significant improvement in their knee-related quality of life than saline injections or at-home knee exercises.

## METHODS

A Double-Blind Randomized Controlled Trial used in this studied. Dr. Moewardi Public Hospital Institutional Review Board approved the conduct of the study with ethical approval number 2.223/XII/HREC/2023. Adult participants aged 60 and over were recruited from RSUD Kota Banjar in West Java for this study, which took place from February to November 2023. They were then followed for nine months. Inclusion criteria were a) a diagnosis of Knee OA based on the American College of Rheumatology, b) a history of moderate-to-severe knee pain for at least three months, as defined by a score of three or higher (0 to 6 ordinal response scale) on the question, "Over the past week, what is the average severity of your left or right knee pain?", c) identification of knee OA by a radiologist on an existing knee radiograph obtained within two years of enrolment and d) tenderness of one or more anterior knee structures on physical examination.

Exclusion criteria encompassed the following conditions: pregnancy, diabetes, anticoagulation therapy, history of total knee replacement, previous knee prolotherapy, any knee injection within 3 months, opioid use, allergy or intolerance to medication, body mass index (BMI) ≥40 kg/m$^2$, and severe comorbidity causing participant unable to conduct exercising at home or showing up for injection visits on time. Each knee's eligibility was evaluated independently. Individuals who met the eligibility requirements consented to participate and were enrolled.

The participant was determined by Federer's formula (n-1) x (t-1) ≥15; (n, sample size of each group; t, number of groups).[12] Results showed that n ≥ 8.5, indicating nine patients in each group. The subjects were randomized by computer-generated randomization to receive injections of either saline (n = 9) or dextrose (n = 9) or to perform knee exercises at home (n = 9). Group participants and the result assessor were blinded about participants' group status. At each injection session, the blinding of the assessor and injection group participants was evaluated by asking them to identify the participant's group assignment using the options "dextrose," "saline," or "don't know." To describe the sample and assess it as a covariate for statistical analysis, baseline data on demographics, self-reported height and weight, and the degree of knee OA as visible on radiographs were gathered and evaluated according to 1-to-4-point Kellgren-Lawrence knee OA scoring method, by the hospital radiologist (A.B.A).

### Injection intervention

Injections were given at 1, 4, and 7 weeks, with optional follow-up sessions at weeks 11 and 15, based on the doctor's consideration (S.K.P.). The Hospital's Pharmacy Center, located off-site, prepared dextrose and saline syringes before hand. They were blinded using an opaque paper sleeve. The injector (S.K.P.) assessed the knee, noted sore anterior knee regions, applied 2% lidocaine skin wheels for anesthetic purposes, and carried out extra- and intra-articular injections (Table 1). After the injection, participants were instructed to rest their knees for two to three days before gradually returning to regular activities. All three groups also consumed 500 mg paracetamol t.i.d. up to one week after weeks 1, 4, and 7.

### At-home knee-exercise

An instructional leaflet regarding knee OA (Visual Health Information, at http://www.vhikits.com/Default.aspx) was given to participants in the exercise group.[13] It included ten at-home knee exercises that the study coordinator had demonstrated before the commencement of the study. Exercises (3 sessions per week, one session daily, 10 repetitions each) were recommended for participants to start, and they were instructed to progressively

increase therapy as tolerated over 7 weeks (5 sessions per week, 3 times daily, 15 repetitions per exercise) if wanted.

### Adherence and Precautions

Call reminders were utilized to motivate and evaluate adherence to the exercise group at the same interval as injection sessions. Each time, a group member was advised not to strain or overuse their knees.

### Outcome measurement

The primary outcome of this study is to assess the severity of OA by measuring pain, stiffness, and function subscales to assess OA severity by the Western Ontario McMaster University OA Index (WOMAC), a validated questionnaire. Its three subscale scores span from 0 (worst) to 96 (best), with a minimum 12-point change as the minimal clinical significant difference (MCID) of WOMAC.[14]

The secondary outcome measure is the knee pain scale (KPS). This validated questionnaire assesses the frequency and severity of knee pain (0 to 4 on an ordinal scale), with higher scores denoting worsening symptoms. 15 Independent KPS data sets were gathered for treated and untreated knees. The WOMAC and KPS scores were obtained in person at baseline before the procedure.

At 21 weeks, all participants were asked a follow-up question on treatment satisfaction: "Would you recommend the therapy you received in this study to others with knee OA like yours?" (Yes/No). Every participant had the opportunity to share qualitative remarks on their experiences.

### Statistical analyses

At each evaluation week, 4, 7, 11, and 21, IBM SPSS version 22.0 for Windows performs a one-way ANOVA analysis for the mean ± SD of the three groups; significant results are further analyzed by posthoc. $P$ value <0.05 indicated a statistical significance level.

## RESULT AND DISCUSSION

Table 2 indicates that there were no significant baseline differences across the groups. The baseline WOMAC scores, x-ray reports, and overall inclusion criteria suggest that, on average, all patients had moderate severity of knee OA according to the Kellgren-Lawrence scores ranging from mild to severe. According to an analysis of the WOMAC subscale scores, D10 participants generally reported steady improvement for 21 weeks, reaching near-maximum improvement by 11 weeks. The function subscale showed the most significant increases; at 21 weeks, D10 participants reported 17.09 points, compared with 7.59 ($P$ = 0.001) and 9.27 points ($P$ =.002) for saline and exercise participants, respectively (Table 3 and Figure 1). Four people in the home exercise program, three saline participants, and the entire D10 said they would recommend their respective therapies.

These results align with single-arm prospective research (N = 36) that used comparable eligibility requirements and the same injection procedure.[10] Participants in that study reported similar overall effects on WOMAC and KPS outcome measures at 52 weeks despite being slightly more symptomatic at baseline. Significant improvement was also seen in the uninjected

TABLE 1
**Intra- and extraarticular injections of D10 and saline**

| Injection | Details | Injection Approach |
|---|---|---|
| D10 | | |
| Intraarticular | 10 cc syringe containing:<br>6 cc D10<br>4 cc lidocaine 2% | Inferomedial approach injection of 10 cc solution |
| Extraarticular | 21 cc distributed into 3 syringes (7 cc each) containing:<br>5 cc D10<br>2 cc lidocaine 2% | The skin-sliding (withdrawal-reinsertion without puncture site removal) of 25G needle injected D10 at 3 insertions (7 cc for each site) of bone ligament. |
| Saline | | |
| Intraarticular | 10 cc syringe containing:<br>6 cc saline<br>4 cc lidocaine 2% | Similar to the abovementioned intraarticular approach. |
| Extraarticular | 21 cc distributed into 3 syringes (7 cc each) containing:<br>5 cc saline<br>2 cc lidocaine 2% | Similar to the abovementioned extraarticular approach. |

D10, 10% Dextrose, G, gauge.

TABLE 2
**Baseline characteristics according to the intervention group**

| Variable | D10 (n = 9) | Saline (n = 9) | Exercise (n = 9) | *P* value |
|---|---|---|---|---|
| Sex, n (%) | | | | |
| Male | 3 (33.3) | 4 (44.4) | 5 (55.6) | 0.73 |
| Female | 6 (66.7) | 5 (55.6) | 4 (44.4) | 0.64 |
| Age, mean (±SD), years | 65.7 (4.8) | 66.1 (5.9) | 65.9 (5.1) | 0.93 |
| Pain onset, mean (±SD), months | 49 (5.5) | 45 (4.2) | 46 (3.9) | 0.09 |
| BMI, n (%), kg/m$^2$ | | | | |
| ≤ 25 | 1 (11.2) | 0 (0.00) | 1 (1.2) | 0.28 |
| 25–30 | 3 (33.3) | 2 (22.2) | 4 (44.4) | |
| ≥ 30 | 5 (55.5) | 7 (77.8) | 4 (44.4) | |
| History of knee therapies, n (%) | | | | |
| Injection of hyaluronic acid | 2 (10.53) | 1 (5.55) | 3 (13.04) | 0.75 |
| Injection of corticosteroid | 4 (21.05) | 3 (16.67) | 3 (13.04) | 0.68 |
| Glucosamine | 7 (34.21) | 6 (33.34) | 8 (34.78) | 0.52 |
| Physiotherapy | 7 (34.21) | 8 (44.44) | 9 (39.14) | 0.19 |
| Kellgren-Lawrence OA grade | | | | |
| 1–2 (mild) | 4 | 3 | 3 | 0.91 |
| 3–4 (moderate–severe) | 5 | 6 | 6 | 0.86 |
| WOMAC, score (SD) [range][a] | | | | |
| Pain | 65.2 (14.1) [34.8 – 91.9] | 65.9 (15.8) [30.9 – 96.1] | 61.9 (12.5) [34.5 – 89.3] | 0.31 |
| Stiffness | 56.9 (18.8) [24.4 – 88.6] | 53.5 (16.9) [23.9 – 86.2] | 53.9 (17.3) [10.8 – 97.5] | 0.07 |
| Function | 64.3 (15.5) [39.4 – 97.1] | 66.2 (17.3) [34.9 – 98.5] | 60.2 (11.5) [36.2 – 87.1] | 0.29 |
| KPS, score (SD)[b] | | | | |
| Frequency | 2.7 (0.7) | 2.1 (0.9) | 2.4 (0.9) | 0.28 |
| Severity | 1.7 (0.7) | 1.8 (0.7) | 1.7 (0.8) | 0.72 |

D10, 10% dextrose; SD, standard deviation; BMI, body mass index; OA, osteoarthritis;
WOMAC, Western Ontario McMaster University OA Index; KPS, knee pain scale.
[a]The higher score in this study indicates better knee-related quality of life. The theoretical range is 0 to 100.
[b]Higher scores indicate worse symptoms. The theoretical range of severity scores is 0 to 5, and the frequency range is 0 to 4.

contralateral knees, indicating that dextrose prolotherapy for more symptomatic knee OA may also improve the uninjected side, probably by reducing compensatory mechanisms.[10]

The direct prolotherapy mechanism generally occurs in four stages, as shown in Figure 2. When the body suffers tissue damage, it initiates a healing process through an inflammatory cascade. However, specific tissues such as ligaments, tendons, cartilage, and fibrocartilage (like the meniscus and labrum) often have limited or no blood supply, making natural healing difficult.[16] In such cases, prolotherapy is employed to encourage the healing process. Prolotherapy encourages healing through inflammation. A cellular response occurs once prolotherapy solutions are injected into the injured area. Various cells, including fibroblasts,

TABLE 3
**WOMAC and KPS subscale score changes**

| Outcomes | Week 4 | Week 7 | Week 11 | Week 21 |
|---|---|---|---|---|
| WOMAC | | | | |
| Pain | | | | |
| D10 | 8.09 (3.28) | 13.89 (3.43) | 10.98 (3.52) | 15.32 (3.51) |
| Saline | 3.01 (2.78) | 5.12 (3.33) | 5.70 (3.46) | 6.31 (3.33) |
| Exercise | 3.90 (3.05) | 2.99 (3.52) | 4.91 (3.65) | 7.92 (3.53) |
| *P* value | 0.06 | 0.03[a] | 0.04[b] | 0.02[a] |
| Stiffness | | | | |
| D10 | 6.98 (4.39) | 14.25 (4.51) | 13.25 (4.52) | 14.90 (4.23) |
| Saline | 8.52 (4.42) | 9.32 (3.98) | 11.98 (4.78) | 11.01 (4.60) |
| Exercise | 3.71 (4.50) | 0.21 (3.27) | 3.09 (4.81) | 8.09 (4.96) |
| *P* value | 0.09 | 0.01[c] | 0.04[b] | 0.07 |
| Function | | | | |
| D10 | 8.55 (3.19) | 13.32 (3.25) | 14.29 (3.33) | 17.09 (3.12) |
| Saline | 3.96 (3.30) | 6.01 (3.36) | 6.50 (3.41) | 7.59 (3.36) |
| Exercise | 4.98 (3.24) | 3.94 (3.41) | 4.92 (3.39) | 9.27 (3.53) |
| *P* value | 0.11 | 0.02[a] | 0.03[a] | 0.04[a] |
| KPS | | | | |
| Frequency | | | | |
| D10 | -0.52 (0.19) | -0.82 (0.24) | -0.86 (0.26) | -1.20 (0.26) |
| Saline | -0.23 (0.21) | -0.31 (0.23) | -0.33 (0.24) | -0.46 (0.24) |
| Exercise | -0.16 (0.23) | -0.23 (0.25) | -0.14 (0.28) | -0.48 (0.26) |
| *P* value | 0.23 | 0.01[d] | 0.01[d] | 0.03[d] |
| Severity | | | | |
| D10 | -0.23 (0.24) | -0.47 (0.24) | -0.53 (0.25) | -0.93 (0.24) |
| Saline | -0.09 (0.24) | -0.20 (0.24) | -0.15 (0.26) | -0.24 (0.26) |
| Exercise | -0.10 (0.25) | -0.14 (0.23) | -0.08 (0.25) | -0.31 (0.24) |
| *P* value | 0.07 | 0.13 | 0.06 | 0.01[d] |

D10 (n =9), saline (n = 9), and exercise group (n = 9) without loss to follow-up, mean (SD). D10, 10% dextrose; SD, standard deviation; BMI, body mass index; OA, osteoarthritis; WOMAC, Western Ontario McMaster University OA Index; KPS, knee pain scale.

[a] D10 surpassed saline and exercise (both $P<0.05$), with no significant differences between saline and exercise ($P>0.05$).

[b] D10 surpassed exercise ($P<0.05$), with no significant differences between saline vs. D10 and saline vs. exercise (both $P>0.05$).

[c] D10 surpassed exercise ($P<0.05$), and saline surpassed exercise ($P<0.05$), with no significant differences between D10 vs. saline ($P>0.05$).

[d] D10 score change was more than saline and exercise score change (both $P<0.05$), with no significant difference between saline vs. exercise score ($P>0.05$).

endothelial cells, and myofibroblasts, form new blood vessels and eventually produce collagen, strengthening and repairing the tissue.[17] The last stage of healing is tissue remodeling. The tissue continues to reshape for several months following an injury or prolotherapy. The new tissue that forms closely resembles and functions like the original tissue before the injury. The associated pain diminishes as the tissue regains strength comparable to the original.[18] Thus, in OA patients, mechanical-induced remodeling may be more destructive than irritative

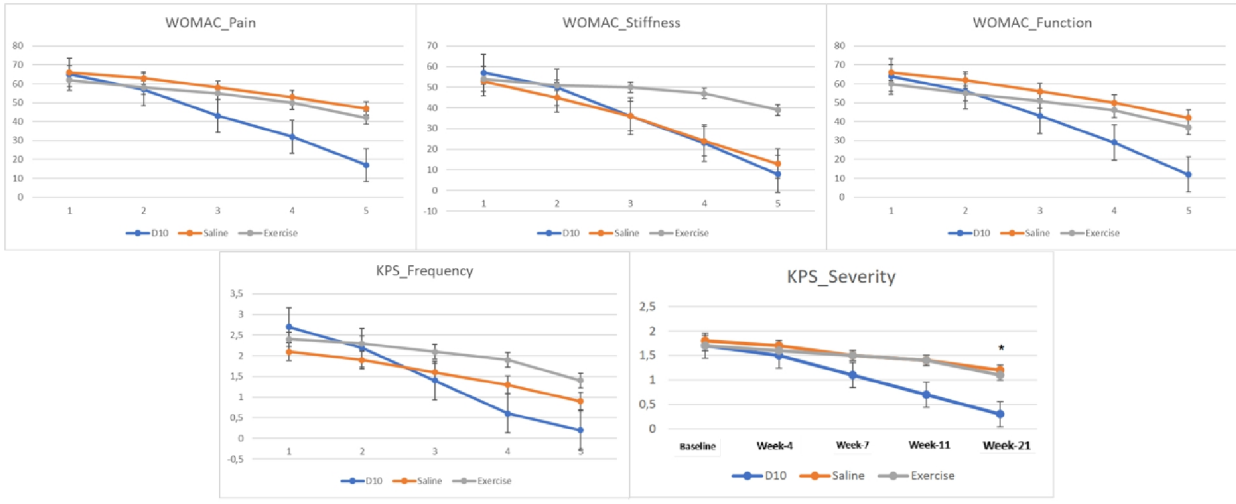


**Figure 1.** The overall group demonstrated WOMAC and KPS-associated line declines, with significant details in Table 3. The changes within week 1–4 in WOMAC and KPS subscale outcomes among D10 (n =9), saline (n = 9), and exercise group (n = 9) were without loss to follow-up.

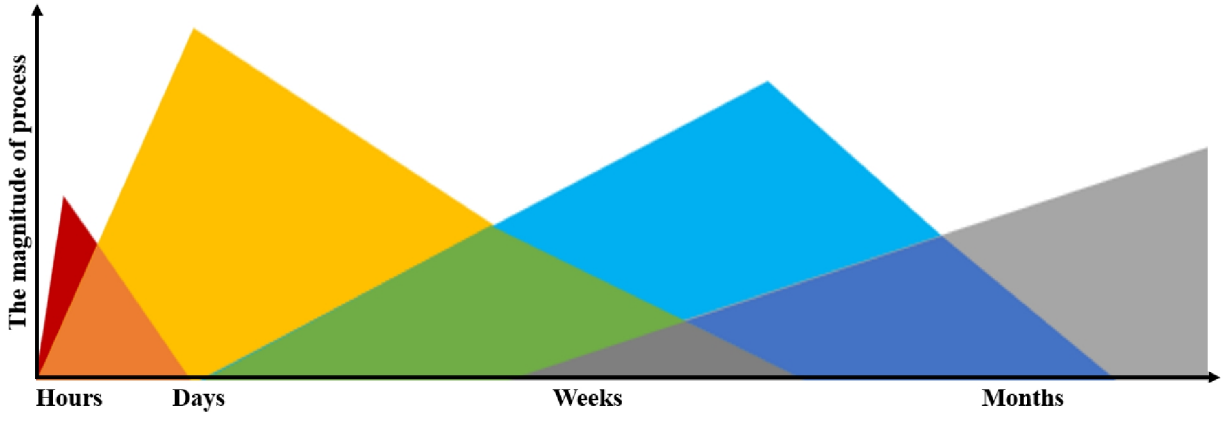


**Figure 2.** The biological process of prolotherapy treatment**.** Bleeding (red), inflammation (yellow), proliferation (blue), and remodeling (grey). Prolotherapy usually lasts four to six weeks to achieve a minimum practical effect.

substance-induced remodeling, such as that utilized in dextrose prolotherapy because mechanical loading can exacerbate the condition of tissues that are already vulnerable to mechanical damage.[19]

Despite the research conducted to date, the exact mechanism of dextrose prolotherapy remains unclear. Researchers have proposed three possible processes.[20] The core concept behind prolotherapy is to promote tissue regeneration and repair by using irritants to induce inflammation. According to one study, 10% dextrose appears to help heal articular cartilage abnormalities in rabbits.[20] Researchers have demonstrated that encouraging the growth of fibroblasts with 20% dextrose has a healing effect on damaged Achilles tendons in rats.[21] Additionally, there is conflicting data regarding the pro-chondrogenic potential of dextrose prolotherapy. Through direct arthroscopic visualization and cartilage biopsy, it was found that intra-articular dextrose prolotherapy improved knee cartilage quality in a manner consistent with chondrogenesis.[22]

Furthermore, dextrose may have a direct pain-modulating effect, which may have a direct impact. In a double-blind, randomized controlled trial involving patients with persistent low back pain accompanied by either gluteal or leg discomfort, caudal epidural dextrose of 5% dextrose, administered without local anesthetic, resulted in a reduction of pain. Notably, analgesia began to take effect as soon as 15 minutes after the injection, supporting the hypothesis that dextrose can have a sensorineural direct impact.[23]

This study has several limitations, including a tiny sample size. However, the effect size of prolotherapy is significant enough to identify differences between the groups. The sample size was inadequate for identifying uncommon side effects, such as drug intolerance or infrequent complications related to injections. This investigation did not compare prolotherapy with the most intervention used, such as intraarticular corticosteroid and hyaluronic acid injections. Confirmation in a more significant effectiveness study, including biomechanical and imaging outcomes, will be necessary to evaluate the potential for disease modification and determine prolotherapy's clinical value.

## CONCLUSION

Based on our findings, prolotherapy injection significantly improved knee osteoarthritis symptoms compared to saline and exercise interventions. Patients in the D10 group exhibited a more significant reduction in WOMAC scores ($p < 0.05$), indicating better pain relief and functional recovery. Additionally, the KPS subscale outcomes showed a substantial enhancement in physical performance among prolotherapy recipients ($p < 0.05$), suggesting its potential as an effective therapeutic option for elderly patients with knee osteoarthritis. Given these results, prolotherapy could be considered a viable non-surgical intervention, particularly for individuals seeking pain management and functional improvement. Further studies with larger sample sizes and extended follow-up periods are recommended to confirm these findings and explore long-term benefits.

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