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Functional outcome in knee osteoarthritis after dextrose prolotherapy intervention: A severity-based pilot study

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ABSTRACT

Background: Osteoarthritis currently remains a significant health problem due to its high prevalence and morbidity rate. Radiological examination is still used as a gold standard to determine the severity of knee osteoarthritis by using Kellgren-Lawrence grading. Dextrose prolotherapy has been known to be effective in treating pain in knee osteoarthritis, but none has compared the efficacy between mild and moderate-severe knee osteoarthritis.
Objective: This study aims to compare the effectiveness of prolotherapy based on its radiological and symptomatic severity in knee osteoarthritis.
Methods: In this pre-post study, the participants who underwent dextrose prolotherapy injection (25% intra-articular and 15% periarticular) for three sessions with four weeks intervals were grouped into mild (grade 1-2) and severe (grade 3-4) groups. Participants' functional status was measured with Western Ontario and McMaster Universities' arthritis index scores at baseline and week 12.
Results: A total of 21 patients (average age 61.42 ± 8.33, BMI 26.81± 3.72) received three therapy sessions. Both groups had significantly better Western Ontario and McMaster Universities arthritis index scores than baseline (-22.57± 11.9; p = 0.002 and -15.42 ± 15.75; p = 0.003). All parameters were improved significantly (p <0.05) in both groups, except the stiffness score (p = 0.292; p = 0.057). There were no differences in functional outcome improvements in both groups (p > 0.05; CI 95%: -21.3 – 7.05).
Conclusion: Prolotherapy effectively improves functional outcomes in all stages of knee osteoarthritis.

Latar Belakang: *Osteoartritis saat ini masih menjadi masalah kesehatan yang signifikan karena prevalensi dan angka morbiditasnya yang tinggi. Untuk menentukan derajat keparahan osteoartritis lutut, pemeriksaan radiologi masih digunakan sebagai baku emas dengan menggunakan grading Kellgren-Lawrence. Proloterapi dekstrosa telah diketahui efektif dalam mengobati nyeri pada osteoartritis lutut tetapi tidak ada yang membandingkan kemanjuran antara osteoartritis lutut ringan dan sedang-berat.*
Tujuan: *Tujuan dari penelitian ini adalah untuk membandingkan efektivitas proloterapi berdasarkan tingkat keparahan radiologis dan gejalanya pada osteoartritis lutut.*
Metode: *Pada penelitian pre-post ini, partisipan yang menjalani injeksi proloterapi dekstrosa (25% intraartikular dan 15% untuk periartikular) selama tiga sesi dengan interval 4 minggu dikelompokkan menjadi ringan (grade 1-2) dan berat (kelas 3-4) kelompok. Status fungsional peserta diukur dengan skor* Western Ontario and McMaster Universities arthritis index *pada awal dan minggu ke-12.*
Hasil: *Sebanyak 21 pasien (usia rata-rata 61,42 ± 8,33; IMT 26,81 ± 3,72) mendapatkan 3 sesi terapi. Kedua kelompok memiliki skor skor* Western Ontario and McMaster Universities arthritis index *yang secara signifikan lebih baik daripada baseline (-22,57 ± 11,9; p = 0,002 dan -15,42 ± 15,75; p = 0,003). Semua parameter meningkat*

secara signifikan (p <0,05) pada kedua kelompok, kecuali skor kekakuan (p = 0,292; p = 0,057). Tidak ada perbedaan peningkatan outcome fungsional pada kedua kelompok (p > 0,05; CI 95% : -21,3 – 7,05).
Kesimpulan: *Proloterapi efektif untuk meningkatkan outcome fungsional pada semua stadium osteoartritis lutut.*

INTRODUCTION

Musculoskeletal disorder is the most common cause of morbidity globally, impacting health and quality of life. Knee osteoarthritis (OA), in particular, is a major problem due to its high prevalence and morbidity rate.[1] Globally, OA affects 240 million people and is present in 10% and 18% of males and females over 60, respectively.[2] Nationally, 7.3 % of the Indonesian population suffers from this disease, and it continues to evoke disability, reduce the quality of life, and even contribute to mortality within the population.[3,4]

The clinical manifestations of OA, such as pain, stiffness, and functional limitation, are largely attributed to the pathological change in joint and periarticular soft tissue.[2] To assess the severity of OA, a radiological examination is typically performed using a genu X-ray anteroposterior (AP) and lateral projection. This method is considered the gold standard and uses the Kellgren-Lawrence (KL) grading system to determine the severity of the condition. The grading system is aligned with the symptomatic severity of the participants.[5]

Upon diagnosis, International Rheumatology Guidelines recommend corticosteroid and hyaluronan injection as pharmacological therapy for knee OA.[6–9] Corticosteroid injection has been associated with many adverse events, such as toxicity to articular cartilage, significantly greater cartilage volume loss with no significant difference in knee pain and accelerated osteoarthritis progression.[10–12] Meanwhile, hyaluronan tends to pose a higher price than other nonoperative modalities, which are commonly used, without any significant effect compared to a placebo in knee OA.[13]

To overcome the issues associated with conventional modalities, other therapeutic approaches have been developed for implementation in knee OA. Prolotherapy is an injection-based therapy that administers certain substances into the intraarticular and periarticular area to repair and restore the function of articular soft tissues.[14] Aside from being effectively similar for tissue regeneration, prolotherapy was also cost-effective compared to platelet-rich plasma (PRP) or stem cells, with hypertonic dextrose as the most common injected substance due to its widely known effectivity.[14,15] Recently, the dextrose prolotherapy (DPT) approach was shown to be effective in reducing pain and disability for mild or moderate to severe knee OA.[14,16,17]

Although previous studies have shown the effect of DPT in mild to moderate knee OA, none has compared the efficacy between mild and moderate to severe knee OA. Therefore, this study aimed to compare the effectiveness of DPT based on its radiological and symptomatic severity in knee OA.

METHODS

Participants

We obtained ethical approval from the University Ethics Committee (protocol number UH19100814) and obtained written informed consent from participants or their legal guardians to participate in our study. This was a prospective cohort study, with participants recruited based on our predetermined inclusion and exclusion criteria. To be eligible for the study, participants had to be adults aged over 40 years who had been diagnosed with knee osteoarthritis according to the American College of Rheumatology (ACR) 2012 criteria and had received a KL grading of 1-4 through radiological examination. Grade 4 participants were required to provide consent to refuse surgery in order to be included in the trial. We excluded participants who had received any previous intra-articular injection, had taken non-steroidal anti-inflammatory drugs (NSAIDs) within one week prior to the intervention, or had contraindications for prolotherapy such as abscesses, cellulitis, or septic arthritis.

Baseline information collected includes age, gender, body mass index, radiological KL grade, history of previous treatment, and comorbidities (systemic disease, including diabetes mellitus, hypertension, gout arthritis and chronic kidney disease). Based on the KL grading, the participants were divided into two groups: mild (KL grade 1-2) as group A and severe (KL grade 3-4) as group B. All participants received functional

status assessments using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score.

Dextrose Prolotherapy Intervention

The DPT intervention was administered to all participants. Prolotherapy typically employs hypertonic dextrose (D-glucose) as the injectant, ranging from 10% to 25%. Based on the recommendation of a previous systematic review, participants received a 5 mL intra-articular injection of 25% dextrose and a 30-40 mL periarticular injection of 15% dextrose.[18] Dextrose is a normal component of blood chemistry and can be safely administered in large doses, making it an ideal proliferate.[19] Some studies suggest that a 25% dextrose solution is most suitable for intra-articular knee injections.[18] Injections were administered in various sites, including the medial collateral ligament, pes anserine, tibial tubercle, coronary ligament, patellar edge, lateral collateral ligament, and tibiofibular ligament. Injection sessions were conducted in weeks 1, 5, and 9, consistent with recommendations for injections delivered every 1 to 8 weeks for 1-5 sessions.[18,20] Participants were instructed to take only acetaminophen (500 mg every 8 hours as needed) if they experienced pain flare-ups and to avoid non-steroidal anti-inflammatory drugs during the first 72 hours after injection. Prolotherapy stimulates the normal tissue healing and repair response, involving three stages: inflammation, proliferation, and tissue remodeling. The use of NSAIDs can impede the healing process.[21]

Outcome

The functional outcome of this study was evaluated using the WOMAC score. Baseline and week 12 WOMAC scores were collected because it is believed that collagen increases, cells mature, and extracellular matrix stiffness forms between weeks 2 and 4, after which the process plateaus.[22] Therefore, improvement in functional outcome is expected to correspond with the improvement of cartilage that occurs within 2-4 weeks after the last injection. A trained research assistant verbally administered the questionnaire to assess the severity of osteoarthritis using the pain, stiffness, and function subscales. The WOMAC composite score, which is the weighted average of the three subscale scores, ranges from 0 (no limitation) to 96 (worst disability).

Analysis

To determine the effectiveness of prolotherapy, the WOMAC scores before and after the intervention in both groups were analysed using the Wilcoxon test. The WOMAC scores of Group A and Group B were compared using an independent t-test.

RESULTS

Participants' characteristics in both group

Out of the 29 participants screened initially, three did not meet the inclusion criteria, and one refused the injection, resulting in 25 participants being enrolled in the study. Group A had eight participants, and Group B had 17 participants. However, four participants were excluded from the analysis because they did not complete the study. Three participants were lost to follow-up, and one participant experienced pain and massive effusion before their second appointment due to heavy activity. Therefore, 21 participants were included in the final analysis, of which 18 were female and three were male, with an average age of 61.42 ± 8.33 years (range: 46–76 years) (Table 1). Seven participants were in Group A, and 14 participants were in Group B, based on KL criteria.

Before treatment, the mean total WOMAC of all participants was 36.76 ± 10.12. Specifically, the mean pre-intervention WOMAC subcategories for pain, stiffness, and physical function were 7.28 ± 2.95; 2.42 ± 2.11; and 27.04 ± 8.24, respectively. At the end of week 12, the mean total WOMAC decreased by 48% to 18.95 ± 12.41 ($p < 0.001$; 95%: 10.37-25.20) (Table 2). The other parameters' scores, namely pain, stiffness, and physical function, also decreased significantly by 63%, 47%, and 44% (Table 1).

Functional changes following prolotherapy in group A

Seven participants in Group A demonstrated significant improvement in most functional outcome parameters, except for stiffness score. The mean baseline total WOMAC score was 39.42 ± 10.13, while the WOMAC subcategories of pain, stiffness, and physical function were 7.14 ± 2.79, 3.20 ± 1.60, and 20.00 ± 8.85, respectively. After three injection sessions, the final total WOMAC score decreased by 57% to 16.85 ± 14.71. There

was also a significant improvement in the WOMAC subcategories of pain and physical function, with a point change of 4 and 8.43, respectively (Table 2).

Functional change following prolotherapy in group B

Nine participants were included in group B. The WOMAC and its subcategory parameters

Table 1. Baseline characteristics of participants

Category	Total	Group A	Group B	p-value*
Number	21	7	14	
Sex†, Female	18	6	12	
Age†				
<50	2 (10.5)	1 (14.3)	1 (7.1)	
>=50	19 (89.5)	6 (85.7)	13 (92.9)	
Average‡	61.42 ± 8.33	58.0 ± 7.65	63.14 ± 8.38	0.172
Weight (kg)‡	65.05 ± 10.81	64.50 ± 6.89	65.3 ± 12.6	1.000
BMI (kg/m2)‡	26.81 ± 3.72	26.16 ± 1.94	27.13 ± 4.40	0.494
Pre WOMAC‡				
Total	36.76 ± 10.12	39.42 ± 10.13	35.42 ± 10.23	0.360
Pain	7.28 ± 2.95	7.14 ± 2.79	7.35 ± 3.12	0.799
Stiffness	2.42 ± 2.22	3.2 ± 1.60	2.00 ± 2.25	0.079
Physical Function	27.04 ± 8.24	20.00 ± 8.85	26.07 ± 8.09	0.535
Comorbidities				
Diabetes Mellitus	4	0	4	
Hypertension	14	3	11	
Gout Arthritis	3	1	2	
Chronic Kidney Disease	1	1	0	

WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index of the severity of osteoarthritis symptoms. * = p-value for Mann-Whitney test; † = number (percentage); ‡ = mean ± SD. Group A: mild group (KL grade 1-2); Group B: moderate-severe (KL grade 3-4)

Table 2. Baseline and score changes in WOMAC score in both groups.

	Baseline	At week 12	Score changes[a]	p-value[a]*	Score changes[b]	p-value[b]
Total WOMAC						
Group A	39.42 ± 10.13	16.85 ± 14.71	-22.57 ± 11.9	0.018*	-7.14 ± 6.78	0.305
Group B	35.43 ± 10.23	20.00 ± 11.56	-15.43 ± 15.75	0.003*		
Pain WOMAC						
Group A	7.14 ± 2.79	3.14 ± 3.13	-4.00 ± 2.94	0.027*	0.92 ± 1.49	0.541
Group B	7.36 ± 3.12	2.43 ± 2.20	-4.92 ± 3.33	0.001*		
Stiffness WOMAC						
Group A	3.2 ± 1.60	2.14 ± 1.95	-2.28 ± 1.49	0.292	-1.14 ± 0.87	0.205
Group B	2.00 ± 2.25	0.86 ± 1.09	-1.14 ± 12.63	0.057		
Physical Function WOMAC						
Group A	20.00 ± 8.85	11.57 ± 10.21	-17.42 ± 8.10	0.018*	-8.07 ± 5.27	0.143
Group B	26.07 ± 8.09	16.71 ± 10.24	-9.35 ± 3.37	0.022*		

[a]Within group; [b]Between groups; *Statistically significant
WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

showed significant improvement, except stiffness score. The mean baseline total WOMAC score was 35.43 ± 2.73, and WOMAC subcategories such as pain, stiffness, and physical function were 7.36 ± 0.83; 2.00 ± 0.60; and 26.07 ± 2.16, respectively.

At the end of week 12, the functional outcomes of these participants were re-assessed. The final total WOMAC score means decreased significantly by a point change of -15.42 ± 15.75 (Table 2). A significant improvement was also shown in WOMAC subcategories of pain and physical function by 66% (2.43 ± 0.59) and 35% (16.71 ± 2.73), respectively. Although the stiffness subcategory also improved by point change, the improvement was insignificant (p = 0.057) (Table 2).

Comparison of WOMAC score mean change in both groups

We compared the effectiveness of prolotherapy for functional outcomes between groups A and B. In group A, the mean total WOMAC score was -22.57 ± 11.9, and for each subcategory (pain, stiffness, and physical function) were -4.00 ± 2.94; -2.28 ± 1.49; and -17.42 ± 8.10, respectively. In group B, the mean total WOMAC score was -15.42 ± 15.75, and for pain, stiffness, and physical function, scores were -4.92 ± 3.33, -1.14 ± 12.63, and -9.35 ± 3.37 (Table 2).

All participants experienced expected mild to moderate post-injection pain within 2-3 days. None of our participants consumed paracetamol to alleviate the pain. There were no other side effects or adverse events.

DISCUSSION

Prolotherapy has been considered a promising injection-based therapy for musculoskeletal disorders, especially knee osteoarthritis. Prolotherapy is a nonsurgical ligament and tendon repairment method that induces low-grade inflammation to promote healing.[23] The current study demonstrates significant improvements in functional outcomes measured by WOMAC score in all groups after prolotherapy injection. It is in line with a previous study that showed significant improvement in NRS score, WOMAC total score, and all subscale scores of WOMAC after 12 weeks of follow-up dextrose prolotherapy injection.[24,25] This finding is similar to a previous report of significantly greater WOMAC score improvement after 18 weeks follow-up with dextrose prolotherapy injection, and was maintained through 52 weeks.[26-28] However, none of the previous studies compared the effectiveness of prolotherapy between mild and moderate-severe knee OA.

We compared functional outcomes between groups A and B and found that both groups showed meaningful enhancement of functional outcomes. Group A has more mean score change than group B in total WOMAC, stiffness, and functional scores. In addition, prolotherapy appeared to be more effective in treating pain in group B than in group A. However, these differences were not statistically significant. It indicates that prolotherapy might be considered an effective and safe nonsurgical regenerative tissue therapy to improve functional outcomes without concern about the radiological grading of knee OA.

There was no significant improvement in stiffness in both group. A possible elucidation is that stiffness in knee OA may result from instability and joint laxity complications. Those are some underlying pathological damages which happen in knee OA. Patients with severe knee OA may use heavier quadriceps and hamstring muscle forces to compensate for their conditions. Higher quadriceps and hamstring muscle forces might stimulate co-contraction with the gastrocnemius muscle, leading to higher joint contact forces. Therefore, higher joint contact force potentially accelerates the progression of cartilage damage.[29] An increase in dynamic joint stiffness and cartilage deterioration due to higher joint contact force may aggravate knee OA, particularly for the stiffness symptom.[30] Therefore, we conclude that the minor improvement in stiffness symptoms of knee OA participants may result from this condition.

Prolotherapy has been proven effective in improving functional outcomes in all stages of knee OA. The enhancement of functional activity is caused by pain improvement and is unrelated to radiological staging.[31,32] A possible reason is that ligament disruption is the leading cause of knee pain. Ligaments have nerve endings and poor vascularisation due to inadequate ligament healing process.[33] Dextrose prolotherapy with a concentration of more than 10% can encourage inflammatory processes by inducing an osmolarity difference between intra- and extracellular compartments.[34] Higher extracellular

concentrations caused fluid transfer and cellular dehydration, eventually leading to lysis. The substances released from the cellular lysis process will stimulate inflammatory responses by inducing growth factors, such as platelet-derived growth factor, transforming growth factor-beta, epidermal growth factor, basic fibroblast growth factor, and insulin-like growth factor. These growth factors then stimulate fibroblast activity to establish mature collagen and improve the healing process of ligaments and tendons, leading to pain improvement.[33,34]

To our knowledge, this is the first study that examines the effectiveness of prolotherapy based on the severity of knee OA. The results of this study may be useful for future decision-making regarding the best treatment for the various grades of knee OA. Our results demonstrate that all grades benefit from this therapy, which might be a viable alternative to surgery. Additionally, because of the cost-effectiveness of prolotherapy injections, this study can also benefit knee OA therapy in low-resource settings. However, in order to confirm the results, further research is required using a larger sample size and a longer observation period towards the long-term outcomes of prolotherapy.

CONCLUSION

Dextrose prolotherapy might be considered a safe and effective alternative injection therapy in all grading of knee OA.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest concerning this study.

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