Effectiveness of dextrose prolotherapy injection on chronic knee osteoarthritis patients

Rian Nofiansyah1, Dedi Susila1, Prihatma Kriswidyatomo1, Belindo Wirabuana1

ABSTRACT

Background: Osteoarthritis (OA) of the knee is a chronic, degenerative, and disruptive joint condition that frequently reduces quality of life and imposes a significant socioeconomic burden on patients and caregivers. The purpose of this study is to compare pain scale and functional ratings before and after dextrose prolotherapy injection in individuals with persistent osteoarthritis of the knee.

Methods: This study is an observational analytical study using retrospective data involving 61 samples of patients with a diagnosis of knee osteoarthritis based on the clinical criteria of the American College of Rheumatology who were injected with 20% dextrose prolotherapy 6 ml intra-articularly and 12.5% dextrose 6 ml peri-articularly. Each patient was injected with prolotherapy 4 times with an interval of 2 weeks at the same injection point. Patients were evaluated for pain scale and functional score at pre-injection, 6 weeks, and 20 weeks. All data processing was performed using SPSS version 26, with a significance level (p-value) set at 0.05.

Results: Demographic characteristics of this study: subjects aged 45 to 75 years with an average of 62.38 ± 8.14 years. 85.2% of subjects were female, 67.2% of subjects had a BMI ≥25 kg/m2, and 75.4% of subjects experienced pain for more than 1 year. There was a significant difference in pain scale and functional score (p-value <0.05) at pre-injection compared to 6 weeks and 20 weeks.

Conclusion: Dextrose prolotherapy injection is effective in improving pain and functional improvement in patients with chronic knee osteoarthritis patients.

Keywords: Dextrose prolotherapy, Knee osteoarthritis, NRS scale, WOMAC score.

INTRODUCTION

Knee osteoarthritis (OA) is a chronic, progressive, and disabling joint condition that frequently causes a reduction in quality of life and places a major socioeconomic burden on patients and caregivers. Recent research suggests that the pathophysiology of osteoarthritis is more complex than a simple degenerative process. To date, there is no cure for osteoarthritis, and knee OA is incurable save for knee arthroplasty, which is regarded as an effective treatment for the advancing condition but is costly.1

The incidence rate of knee OA cases is 240 per 100,000 people each year. In Indonesia, the prevalence of osteoarthritis rises with age, with 5% in persons under 40, 30% in those 40–60, and 65% in those over 61. The frequency of knee OA is 15.5% in men and 12.7% in women.2

In recent years, several injection-based therapies for knee osteoarthritis have been investigated, including dextrose prolotherapy, ozone, botulinum toxin, platelet-rich plasma (PRP), and hyaluronic acid. Dextrose is an affordable and readily available therapy. Dextrose prolotherapy has emerged as a viable alternative injection therapy for treating persistent pain in musculoskeletal diseases. Although dextrose prolotherapy has been extensively documented to be effective in treating a variety of musculoskeletal disorders, it has yet to be accepted as a main treatment for recent knee OA.3,4 The 2019 American College of Rheumatology/Arthritis Foundation guidelines advocate the conditional use of prolotherapy for individuals with knee osteoarthritis.4

Hypertonic dextrose has been proven in laboratory investigations to increase intracellular expression of growth factors in tenocytes and fibroblasts. Rabago et al. discovered that dextrose injections improved pain relief, edema, episodes of buckling, and flexion range more than lidocaine injections or exercise. Prolotherapy patients improved much more than the control group at the 52-week follow-up.5 The purpose of this study is to compare pain scale and functional ratings before and after dextrose prolotherapy injection in individuals with persistent osteoarthritis of the knee.

METHODS

Study Design and Setting

This study employed an observational analytic design using retrospective data to investigate the differences in pain scale and functional scores before and after intra-articular 20% dextrose prolotherapy and periarticular 12.5% dextrose prolotherapy injections in patients with chronic knee osteoarthritis. Data were collected by reviewing medical records and through telephone interviews. Data collection took place from June to October 2023. The research was conducted at the Gundih...
Community Health Center, Sidotopo Wetan Community Health Center, and Manukan Kulon Community Health Center by examining the medical records and conducting telephone interviews with patients who underwent dextrose prolotherapy injections. Inclusion criteria were: diagnosed with knee OA based on American College of Rheumatology clinical criteria, age 45 – 75 years, no history of knee surgery, willing to do prolotherapy injection, and complete patient data. Exclusion criteria were: undergoing anti-inflammatory, anticoagulant, or immunosuppressive therapy, consumption of NSAIDs within the last 7 days before therapy; uncontrolled diabetes mellitus; severe cardiovascular disease; patients who could not be followed up, and patients who died during the study period.

Statistical Analysis
Descriptive and inferential statistics were employed in this study. Descriptive statistics were used to present demographic data and research variable data. Numeric data with a normal distribution were presented as mean ± standard deviation and median-interquartile for non-normally distributed data. Ordinal and nominal scale data were presented as frequencies and percentages.

This research involved paired numerical comparisons with more than two measurements. If the difference distribution was normal, repeated ANOVA with Bonferroni post hoc tests was used. If the difference distribution was not normal, the Friedman test with Wilcoxon post hoc tests was applied. All data processing was performed using SPSS version 26, with a significance level (p-value) set at 0.05.

RESULTS
Characteristics of Study Subjects
Data were collected by reviewing medical records and through telephone interviews. The sample for this study consisted of patients with OA who underwent intra-articular 20% dextrose prolotherapy and periarticular 12.5% dextrose prolotherapy injections at the Gundih Community Health Center, Sidotopo Wetan Community Health Center, and Manukan Kulon Community Health Center in June – July 2023, and met the inclusion and exclusion criteria. The total sample size obtained was 61 samples, as presented in Table 1.

Based on Table 1, the total sample size is 61 samples. The age characteristic in this study has a mean age of 62.38 years. For gender characteristics, the majority of subjects are female, accounting for 52 subjects or 85.2%. Regarding BMI characteristics, 54.1% of subjects are overweight and 13.1% are obese. The

Table 1. Distribution of Demographic Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Amount n=61</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>45-75</td>
<td></td>
</tr>
<tr>
<td>Reach</td>
<td>62.38 ± 8.14</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Man</td>
<td>9</td>
<td>14.8</td>
</tr>
<tr>
<td>Woman</td>
<td>52</td>
<td>85.2</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>20</td>
<td>32.8</td>
</tr>
<tr>
<td>Overweight</td>
<td>33</td>
<td>54.1</td>
</tr>
<tr>
<td>Obesity</td>
<td>8</td>
<td>13.1</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elementary school</td>
<td>15</td>
<td>24.6</td>
</tr>
<tr>
<td>Junior High School</td>
<td>22</td>
<td>36.1</td>
</tr>
<tr>
<td>Senior High School</td>
<td>16</td>
<td>26.2</td>
</tr>
<tr>
<td>College</td>
<td>8</td>
<td>13.1</td>
</tr>
<tr>
<td>Duration of Pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 6 months</td>
<td>3</td>
<td>4.9</td>
</tr>
<tr>
<td>&lt; 1 year</td>
<td>12</td>
<td>19.7</td>
</tr>
<tr>
<td>&gt; 1 year</td>
<td>46</td>
<td>75.4</td>
</tr>
</tbody>
</table>

Table 2. Description and Normality Test of the Pain Scale

<table>
<thead>
<tr>
<th>Pain Scale</th>
<th>N</th>
<th>*p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before injection</td>
<td>61</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6th week</td>
<td>61</td>
<td>0.007</td>
</tr>
<tr>
<td>20th week</td>
<td>61</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*It is declared to be normally distributed if the p-value is >0.05

Figure 1. Shows a box plot graph of the NRS scale. This graph shows that there is a tendency for the NRS scale to decrease from before injection, the 6th week, and the 20th week.
Analysis of Pain Scale Differences

Based on the results of the normality test using Kolmogorov-Smirnov (shown in Table 2), p-values for the pain scale were < 0.05 before injection, at week 6, and at week 20. This indicates that the distribution of NRS scale data is not normally distributed. Therefore, the Friedman test was used for further NRS scale comparisons to examine whether there is a significant difference in the NRS scale before injection, at week 6, and at week 20. The results are presented in Figure 1.

In Table 3, the Friedman test results for the pain scale before injection, at week 6, and at week 20 yielded a p-value <0.001. This indicates a significant difference in the pain scale before injection compared to week 6 and week 20. The range and median of the NRS scale before injection was 3-10 with a median of 6; the NRS scale at week 6 was 0-6 with a median of 3, and at week 20, it was 0-3 with a median of 2.

Post hoc Wilcoxon analysis in Table 4. Mean and standard deviation values are not reported because in a non-normal distribution of data, mean and standard deviation cannot adequately represent the data. In the post hoc Wilcoxon analysis, the pain scale before injection vs. week 6; before injection vs. week 20; and week 6 vs. week 20, all had p-values < 0.05, indicating a significant difference between the pain scale before injection and the pain scale at week 6; a significant difference between the pain scale at week 6 and the pain scale at week 20; and a significant difference between the pain scale at week 6 and the pain scale at week 20.

Analysis of Functional Score Differences

Functional scores were measured using the WOMAC score, consisting of three subscales: pain subscale, stiffness subscale, and functional subscale. The maximum total score is 96, and the higher the score, the more disruptive the complaints of OA to the patient’s functionality. WOMAC score measurements were taken three times: before injection, at week 6, and via telephone at week 20, as presented in Figure 2.

Based on the results of the normality test using Kolmogorov-Smirnov (Table 5), p-values were 0.2 before injection and 0.2 at week 6, indicating a normal distribution...
of data. However, the p-value at week 20 was 0.005, which is <0.05, meaning that the distribution of functional score data is considered not normally distributed. Therefore, the Friedman test was used for further WOMAC score analysis to examine whether there is a significant difference in WOMAC scores before injection, at week 6, and at week 20.

In Table 6, the Friedman test results for WOMAC scores before injection, at week 6, and at week 20 yielded a p-value < 0.05. Therefore, it can be concluded that there is a significant difference in WOMAC scores before injection, at week 6, and at week 20.

From the results of post hoc Wilcoxon analysis in Table 7, it was found that the functional scores had p-values < 0.05, indicating a significant difference between WOMAC scores before injection and WOMAC scores at week 6; a significant difference between WOMAC scores at week 6 and WOMAC scores at week 20; and a significant difference between WOMAC scores at week 6 and WOMAC scores at week 20.

**DISCUSSION**

This study aimed to investigate the differences in pain scale measured by the NRS scale and functional scores measured by the WOMAC score before and after intra-articular 20% dextrose prolotherapy and periarticular 12.5% dextrose prolotherapy injections in patients with chronic knee osteoarthritis. The age range in this study was between 45 and 75 years, with an average of 62.38 ± 8.14 years. The age in this study is not significantly different from the research conducted by Rabago in 2013, where the average age was 56.7 ± 7.2 years.

In this study, the majority of subjects were female, accounting for 52 subjects or 85.2% of the total subjects. Females are more susceptible to OA. In another study, males had a lower risk of radiographically confirmed knee OA. According to the WHO in 2023, 73% of people with osteoarthritis are over 55 years old, and 60% of them are females. The high incidence of OA in females is suspected to be triggered by a decrease in sex hormone levels in postmenopausal women.

Based on BMI, 67.2% of the subjects were overweight (BMI ≥25 – 29.9 kg/m2) and obese (BMI ≥30 kg/m2). Obesity in women or men with a BMI of 30 to 35 increases the risk of developing OA up to 4 times. Excess weight in obesity leads to increased excessive load on the knee joints, resulting in wear and tear of the joint cartilage, accompanied by ligament damage, and ultimately causing OA.

**Results of the Analysis of Pain Scale Differences in Study Subjects**

Dextrose prolotherapy can benefit people with knee osteoarthritis by stabilizing intra-articular ligaments, which improves joint mechanics, articular cartilage healing, and range of motion. Dextrose is the most often utilized agent or substance for prolotherapy in clinical practice, with concentrations ranging from 12.5% to 25%. Dextrose is regarded as the best proliferant since it is water-soluble, a natural component of blood chemistry, and can be safely injected in huge numbers into various regions. The hypertonic dextrose solution works by drying cells at the injection site, producing local tissue stress and attracting granulocytes and macrophages, which promote recovery.

In this study, the evaluation of the pain scale measured by the NRS showed a significant difference in the NRS scale (p-value < 0.05) before injection compared to week 6 after dextrose prolotherapy injection and week 20 after dextrose prolotherapy injection. This study aligns with the proposed hypothesis, indicating a significant difference in the pain scale before and after intra-articular 20% dextrose prolotherapy and periarticular 12.5% dextrose prolotherapy injections in patients with chronic knee osteoarthritis.

Clinical trials have demonstrated that NRS is more reliable than VAS, especially in less educated patients. The simplicity and ease of determining the pain scale are crucial criteria in pain assessment in clinical conditions, as evidenced by the prevalence of using the NRS 0–10 cm, a straightforward tool to estimate pain levels.

**Results of the Analysis of Functional Score Differences in Study Subjects**

In this study, the functional score used was the total WOMAC score, hereafter referred to as the WOMAC score. The higher the WOMAC score, the more severe the patient’s complaints and the more disruptive their activities. Statistical tests revealed a significant difference in WOMAC scores before and after intra-articular 20% dextrose prolotherapy and periarticular 12.5% dextrose prolotherapy injections (p-value < 0.05). The evaluation of WOMAC scores showed that subjects experienced an improvement in complaints assessed using WOMAC scores, and the effect persisted until week 20. According to another study, significant results were obtained in measurements based on WOMAC within 4 weeks of the first injection and continued to show progressive development during 1 year of monitoring.

Hypertonic dextrose has been proven to increase intracellular expression of growth factors in tenocytes and fibroblasts in investigations. Dextrose prolotherapy can also benefit people with knee OA by stabilizing intra-articular ligaments, which improves joint mechanics, articular cartilage healing, and range of motion.

The working mechanism of prolotherapy has not been clearly outlined, but the current prevailing hypothesis is that the compounds it contains can stimulate the increase of growth factors, including platelet-derived growth factor, transforming growth factor-beta, epidermal growth factor, basic fibroblast growth factor, insulin-like growth factor, and connective tissue growth factor.

These factors stimulate tissue repair by promoting the deposition of collagen fibers. Prolotherapy also has the effect of sclerosis of blood vessels. The formation of new blood vessels correlates with pain, so prolotherapy administration will suppress

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**Table 7. The results of post hoc Wilcoxon analysis**

<table>
<thead>
<tr>
<th>Pain Scale</th>
<th>*p-value</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before injection vs 6th week</td>
<td>&lt;0.001</td>
<td>Meaningful</td>
</tr>
<tr>
<td>Before injection vs 20th week</td>
<td>&lt;0.001</td>
<td>Meaningful</td>
</tr>
<tr>
<td>Week 6 vs week 20</td>
<td>&lt;0.001</td>
<td>Meaningful</td>
</tr>
</tbody>
</table>

*There is a significant difference if the p-value <0.05*
tissue neovascularization and can reduce the patient's perceived pain.12

Rabago et al. discovered that dextrose injections reduced pain, edema, buckling episodes, and flexion range more effectively than lidocaine injections or workouts. Patients receiving prolotherapy also showed significantly higher improvement at the 52-week follow-up than the control group.13

Hmamouchi et al. conducted a crossover research in which individuals were randomly assigned to undergo 32 weeks of exercise therapy combined with dextrose injections at weeks 0, 4, 8, and 12, or dextrose injections alone at weeks 20, 24, 28, and 32. Both groups demonstrated a significant reduction in knee OA symptoms as indicated by WOMAC scores, which remained for six months.14

According to other studies, WOMAC scores experienced a significant decline for up to 3 months and persisted until the 6th month. This may be attributed to the excessive use of the knee after the alleviation of pain complaints and improvement in knee function.15

This study has several limitations, including (1) this study did not compare dextrose prolotherapy injection with other therapies, (2) this study did not mention the side effects that occurred in patients who were injected with prolotherapy due to data limitations, (3) the follow-up time in this study was relatively short. To improve the study, we recommend conducting further research that incorporates knee ultrasound evaluations before and after prolotherapy injections, evaluating the potential side effects of prolotherapy injections, and investigating biomarkers of knee osteoarthritis improvement.

CONCLUSION

There are significant differences in pain scale and functional scores before and after intra-articular injection of 20% dextrose prolotherapy and 12.5% dextrose periarticular in patients with chronic knee osteoarthritis. Moreover, the injection of 20% intra-articular dextrose and 12.5% periarticular dextrose is effective in improving pain and functional scores in patients with chronic knee osteoarthritis. Prolotherapy injection is a highly effective pain intervention for chronic knee osteoarthritis. The materials used in this study are not only inexpensive but also easily obtainable, making them applicable in areas with limited facilities.

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APPROVAL FROM THE HEALTH RESEARCH ETHICS COMMITTEE

This research has obtained approval from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Airlangga, Surabaya. With the ethical clearance letter number No.354/EC/KEPK/FKUA/2023.

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AUTHORS’ CONTRIBUTION

All authors participated in the analysis of the data, the writing process, and the revision of the publication and collectively agreed to take responsibility for all elements of this work.

CONFLICT OF INTEREST

There is no conflict of interest for this study.

REFERENCES
