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RESEARCH ARTICLE

Comparison of the Effectiveness between Oral NSAIDs and Dextrose Prolotherapy in Knee Osteoarthritis

Sugiyanta Sugiyanta,[1] Winie Septhia Dwicahyandari,[2] Erfan Efendi,[1] Desie Dwi Wisudanti[3]

[1]Department of Biochemistry, Faculty of Medicine, Universitas Jember, Jember, Indonesia,
[2]Faculty of Medicine, Universitas Jember, Jember, Indonesia,
[3]Department of Pharmacology, Faculty of Medicine, Universitas Jember, Jember, Indonesia

Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) are the first treatment choice for pain relief in osteoarthritis (OA). However, known to have an 85% risk of side effects on the gastrointestinal and a 40% chance of cardiovascular complications. In addition, in certain classes of NSAIDs, the risk of chronic kidney disease increases due to long-term consumption. On the other hand, dextrose prolotherapy is a regenerative therapy. This study aimed to compare the effectiveness of oral NSAIDs with dextrose prolotherapy in knee OA based on clinical features. This study used an observational method (cross-sectional) conducted in three locations; Jember Clinic Hospital, Balung Hospital, and Harapan Mulya Kertonegoro Jenggawah Clinic from September 2021 to March 2022. Of the 75 population, 23 patients with mild to moderate knee OA were divided into two groups; 15 samples of dextrose prolotherapy and eight samples of oral NSAIDs. Data in the study showed the mean WOMAC score in the dextrose prolotherapy group was 12.4±11.7, while the oral NSAID group was 34.75±17.6. A total of 14 samples experienced a decrease in scores after switching from oral NSAIDs to dextrose prolotherapy. Bivariate analyses were performed using Mann-Whitney and Wilcoxon tests. Both statistical tests show a $p=0.001$ ($p<0.05$). Thus, this study concluded that dextrose prolotherapy was more effective than oral NSAIDs in knee OA.

Keywords: Dextrose prolotherapy, knee osteoarthritis, regenerative therapy

Introduction

Research on Osteoarthritis or Osteoporosis Against Disability (ROAD) by Muraki et al.[1] stated that knee OA was significantly associated with the onset of pain and physical functional disability. In Indonesia, osteoarthritis (OA) is the most common arthritis.[2] Recent research in a book by Rodríguez-Merchán and Gómez-Cardero[3] states that acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) are the first-line pharmacological therapy for OA. On the other hand, NSAIDs are known to have an 85% risk of side effects on the gastrointestinal tract and more than 40% risk of cardiovascular complications.[4–7] Furthermore, a study by Zhang et al.[8] stated that the likelihood of acute kidney injury increased by more than 50% in people exposed to NSAIDs.

Meanwhile, injection is another safe option for OA therapy and has a high satisfaction rate.[9,10] Types of injection tested for efficacy and often used for OA treatment are corticosteroids, hyaluronic acid, and platelet-rich plasma (PRP).[9] PRP is an injection therapy with a tissue regenerative mechanism of action. However, the cost of the procedure tends to be expensive.[11]

Tissue regenerative therapy that is less expensive than PRP is dextrose prolotherapy.[11] Dextrose prolotherapy has been tested in a randomized controlled trial and meta-analysis, showing improved knee pain and function.[12,13] Hypertonic dextrose solutions act by dehydrating cells, causing transient sterile inflammation, attracting granulocytes and macrophages, and inducing healing. This phase is similar to the body's natural healing process, which triggers the release of growth factors and collagen deposition.[14] Dextrose solution has proven effective in treating chronic pain so that it can treat pain.[13] The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was used to detect patients for OA. The WOMAC index is the best validated and most widely used outcome measure in subjects with knee osteoarthritis.[15,16] Rabago et al.[17] report decreased WOMAC scores in the last four weeks after the first injection session and continued improvement up to 52 weeks on dextrose prolotherapy.

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Correspondence: Dr. dr. Sugiyanta, M.Ked. Department of Biochemistry, Faculty of Medicine, Universitas Jember. Jln. Kalimantan No. 37, Kampus Tegalboto, Jember 60293, East Java, Indonesia. E-mail: sugiyanta97.fk@unej.ac.id

Studies on dextrose prolotherapy in treating knee OA have only compared with injections. Studies are comparing oral medication, especially NSAIDs, as the first treatment for OA in the community. Oral NSAIDs were compared with injectable hyaluronic acid in a meta-analysis. There was no significant difference between the continuous use of oral NSAIDs and the injection of hyaluronic acid in knee OA.[18] Further studies that treat OA causatively should be developed to prevent continued exposure to NSAIDs. This study aims to compare the effectiveness of oral NSAIDs with dextrose prolotherapy in knee OA patients.

Methods

This study used an analytical observational method with a cross-sectional design conducted in three locations; Jember Clinic Hospital, Balung Hospital, and Harapan Mulya Kertonegoro Jenggawah Clinic from September 2021 to March 2022. The ethical review has been submitted to the Health Research Ethics Committee, Faculty of Medicine, Universitas Jember. Therefore, it has been declared feasible based on number: 1571/H25.1.11/KE/2022. From the 75 population, 23 patients with mild to moderate knee OA who met the eligibility criteria were divided into two groups, with 15 dextrose prolotherapy samples and eight oral NSAIDs.

The method of determining this sample is by making all members of the population that meet the criteria into a model (total sampling). Patients ≥40 were diagnosed with mild to moderate knee OA based on Kellgren and Lawrence or ultrasound. The patient had a history of taking oral NSAIDs, then continued one type of therapy, switched to prolotherapy, or remained oral NSAIDs. All samples had a history of taking oral NSAIDs. In the dextrose prolotherapy group, the sample switched to dextrose prolotherapy by receiving one injection within 4–52 weeks, while the oral NSAID patient group continued to take the drug continuously. The assessment carried out in this study came from the WOMAC for each study sample. This instrument is a questionnaire to measure functional impairment and pain associated with lower extremity OA. There were five questions related to pain, two to joint stiffness, and seventeen to functional activities. In this questionnaire, a total score of 0–24 has an interpretation of the clinical picture as mild, 24–48 is interpreted as moderate, 48–72 is interpreted as severe, and 72–96 is interpreted as very severe.

Descriptive statistical univariate analysis was carried out to describe the entire sample taken, the description in the form of a graph of age, gender, body mass index (BMI), degree of OA based on Kellgren and Lawrence, and the type of oral NSAID used. In addition, bivariate analysis was carried out using the Mann-Whitney comparison and Wilcoxon tests. The Mann-Whitney test is a non-parametric test with two independent samples; in this case, it compares the WOMAC score of the sample taking oral NSAIDs with the WOMAC score of the sample who switched to dextrose prolotherapy. The Wilcoxon test is a dependent paired non-parametric test to see the decrease or increase in WOMAC scores in the dextrose prolotherapy group.

Results

A total of 23 samples met the eligibility criteria, with details of 15 samples receiving dextrose prolotherapy with a history of taking oral NSAIDs. The eight others never received dextrose

Table 1 Characteristics of Respondents

Characteristics	n=23
Gender	
Male	7
Female	16
Age (years)	
40–50	3
51–60	9
61–70	10
>70	1
BMI (kg/m^2)	
Normal (18.5–24.9)	7
Overweight (25–29.9)	14
Obesity (≥30)	2
OA degree	
Mild	4
Moderate	19
Therapy	
Dextrose prolotherapy	15
Oral NSAIDs	8
Oral NSAIDs	
Ibuprofen	2
Mefenamic acid	4
Meloxicam	7
Sodium diclofenac	9
Celecoxib	1

Table 2 WOMAC Score of Prolotherapy Dextrose Group

WOMAC Interpretation	Pre-injection n=15	Post-injection n=23
Mild (0–24)	0	13
Moderate (24–48)	8	2
Severe (48–72)	6	0
Very severe (72–96)	1	0

Table 3 Comparison of WOMAC Score

WOMAC Interpretation	Oral NSAIDs n=8	Dextrose Prolotherapy n=23
Mild (0–24)	3	13
Moderate (24–48)	3	2
Severe (48–72)	2	0
Very severe (72–96)	0	0

prolotherapy; they only consumed oral NSAID therapy; all respondents completed the WOMAC questionnaire face-to-face and online.

Table 1 describes the characteristics of the research sample. The description is in the form of a distribution table of sex, age, BMI, the degree of OA based on Kellgren and Lawrence, and the type of therapy. The characteristics of the sample are female (16 of 23 respondents), aged 61–70 years (10 of 23 respondents), and the criteria for BMI overweight (14 of 23 respondents) dominate the study sample. Age is a risk factor for various diseases, including knee OA. The aging process is a risk factor related to the pathophysiology of cartilage damage in the knee joint structure; regarding gender, differences in height, weight, and bone size cause women to have lower knee cartilage volumes than men.[19] In knee OA, mechanical overload on the joint causes the knee to hold more weight, contributing to joint damage.[19,20] Researchers do not limit the type consumed. The most commonly used type of NSAID is diclofenac sodium. According to da Costa et al.,[21] diclofenac sodium 150 mg/day is more effective than other NSAIDs.

Table 2 shows a significant difference in the WOMAC scores of the pre-injection sample compared to the post-injection sample. The WOMAC score of this is because thee-injection patients is an assessment when the sample is still taking oral NSAIDs, has a moderate to severe interpretation. Conversely, the WOMAC score interpretation was mild to moderate after switching to dextrose prolotherapy.

When the two groups were compared, the WOMAC scores of the groups continuing oral NSAID therapy were more variable. The data shows that the sample has light, moderate, and heavy interpretations. Meanwhile, there were no samples with severe interpretation in the group that switched to dextrose prolotherapy (Table 3).

Table 4 shows that there are differences between the oral NSAID group and the prolotherapy group. The difference lies in the average WOMAC score. The average value of the

Table 4 Average WOMAC Score

Groups	Average±SD
Oral NSAIDs	34.75±17.6
Dextrose prolotherapy	12.4±11.7

Table 5 Mann-Whitney Test Analysis

Variables	n	Average	Total	U	p Value
Oral NSAIDs	8	17.94	143.5	12.500	0.001*
Dextrose prolotherapy	15	8.83	132.5		

Note: *p value<0.05 significant

Table 6 Wilcoxon Test Analysis

WOMAC Scores	n	Average	Total	Z	p Value
Increase	1	1.00	1.00	3.352	0.001*
Decrease	14	8.50	119.00		

Note: *p value<0.05 significant

oral NSAID group was 34.75±17.6. In contrast, the average value of the dextrose prolotherapy group was 12.4±11.7. Therefore, the mean WOMAC score in the dextrose prolotherapy group was lower.

Table 5 shows the Mann-Whitney test displays p=0.001 (p<0.05), so the hypothesis is accepted. Researchers then performed the Wilcoxon test to see if there was an increase or decrease in WOMAC scores in knee OA patients (Table 6).

Discussion

All samples initially used oral NSAIDs as first-line treatment. Knee OA patients perform this therapy because they cannot stand the perceived pain. Oral NSAID drugs were obtained from the practitioner in charge of the patient; then, the patient stored the drug to be consumed at any time when the pain recurred. Then, the fifteen samples switched to a different type of therapy, namely dextrose prolotherapy. Changes in the kind of therapy are based on the patient's dissatisfaction with oral NSAID treatment. The remainder continued oral NSAID therapy until now. Based on Table 6, one sample experienced an increase in WOMAC scores, while 14 samples experienced a decrease in WOMAC scores after switching to dextrose prolotherapy. A reduction in the WOMAC score means a decrease in the clinical picture based on symptoms of knee OA. Wilcoxon test results show p=0.001 (p<0.05). Based on the results of both statistical tests, the hypothesis in this study was accepted or concluded that dextrose prolotherapy was more effective than oral NSAIDs in knee OA patients.

The interpretation of the respective WOMAC scores obtained was quite diverse in the sample who continued oral NSAID therapy until now. Three of 8 respondents had a mild WOMAC score, 3 of 8 respondents had moderate, and 2 of 8 respondents had severe. The patient stated that the recurrence was recurrent. The patient felt an improvement in his complaints. However, the symptoms reappeared after stopping consumption. Relapse did not occur in the sample group that switched to dextrose prolotherapy. Improvements are progressive. This can be illustrated by 13 of 15 respondents with a mild WOMAC interpretation, while the other 2 of 15 are moderate. Whereas 8 of 15 samples had a moderate interpretation, 6 of 15 were severe, and 1 of 15 had severe interpretations.

Prolotherapy is an injection therapy with long-term continuous improvement.[22,23] In the research of Rabago et al.,[22] a sample of mild to severe knee OA received three prolotherapy injections at weeks 1, 5, and 9. Patients were evaluated at weeks 12, 26, 52, and 2.5 years. The increase in the total WOMAC score was 20.9±22.6 points or 35.6% at 2.5 years. In addition, 40 of 65 participants increased by 12 points or more. Like that research, Sita et al.[13] studied injection therapy in moderate to severe OA (minimum three months) and compared dextrose prolotherapy and normal saline (NS) injected at weeks 0, 4, 8, and 16. As a result, dextrose prolotherapy reduced pain and improved function and quality. Survival compared with NS injection; the beneficial effect persisted for 52 weeks.

In this study, from 15 samples of mild to moderate OA who switched from oral NSAIDs to dextrose prolotherapy, 14 samples showed that prolotherapy with several injections once in 4–52 weeks could reduce WOMAC scores, found a reduction in clinical features based on knee OA symptoms. Prolotherapy can be the treatment for patients with mild to moderate knee OA.

Gallelli et al.,[24] who studied oral NSAIDs in OA, concluded that long-term NSAID treatment is not recommended in patients with OA. Treatment with oral celecoxib, ibuprofen, and diclofenac is effective in the short term to suppress proinflammatory cytokines, reduce pain, and improve function in patients with symptomatic knee OA without serious side effects. Wheaton and Jensen[25] concluded that NSAIDs' initial inhibition of the inflammatory cascade is short-lived in the healing of ligaments, tendons, and bones. interpretations OA of the knee is chronic

and progressive, causing COX-2 expression to occur continuously. COX-2 expression will recur after its inhibitory effect by oral NSAIDs decreases so that the recurrence of symptoms is recurrent.

Meanwhile, dextrose prolotherapy triggers the synthesis of inflammatory mediators that accelerate the regeneration process of damaged tissue, strengthen connective tissue, and improve surrounding tissue biomechanics.[26] The prolotherapy used was 40% dextrose diluted with lidocaine to 25%. The hypertonic fluid renders the inflammatory response sterile, leading to controlled acute inflammation and promoting proliferation.[27]

Further research on prolotherapy is needed, especially in clinical trials. The WOMAC score can be used serially in the same duration to determine the progression of improvement in the clinical features of patients with knee osteoarthritis. Radiographic evaluation of post-therapy assessment in OA can be done to strengthen the results of further studies.

Conclusion

This study concluded that dextrose prolotherapy was more effective than oral NSAIDs in knee osteoarthritis.

Conflict of Interest

The authors certify that they have no affiliation with or involvement in any organization or entity in the subject matter or materials discussed in this manuscript.

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