The effect of hypertonic dextrose prolotherapy on knee osteoarthritis outpatients in Dr. Ramelan Navy Hospital Surabaya: case series

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ABSTRACT

Background: The high use and pressure on the knee cause osteoarthritis to occur frequently. Prolotherapy is a non-surgical injection therapy used to treat chronic pain in musculoskeletal conditions, including knee OA. This solution can create local irritation, inflammation, and tissue regeneration, thereby increasing the strength of damaged ligaments, tendons, and intra-articular structures. Therefore, the aim of this research is to assess the changes in VAS and WOMAC scores, as well as plain radiographs of knee OA patients after hypertonic dextrose prolotherapy.

Methods: This experimental case series was done at the Physical Medicine and Rehabilitation Polyclinic of dr. Ramelan Navy Hospital Surabaya December 2021 to April 2022, by giving hypertonic dextrose prolotherapy injection intraarticularly to 3 knee OA subjects using a 22G or 23G needle. This procedure was performed 3 times on each subject, with an interval of 4 weeks each. The assessments were carried out with VAS and WOMAC scores, as well as plain radiographs of knee OA patients after hypertonic dextrose prolotherapy.

Results: In all 3 subjects, the knee joint spaces were slightly widened on plain radiographs, as well as decreased VAS and WOMAC scores after injection.

Conclusion: Hypertonic dextrose prolotherapy here had minimal side effects, affordable prices, and a fast process. It also causes a reduction in pain and joint stiffness and causes functional improvement. Prolotherapy may be considered a therapy for knee OA patients.

Keywords: hypertonic dextrose prolotherapy, knee osteoarthritis, plain radiograph of the knee, VAS, WOMAC score.


INTRODUCTION

The knee is the largest synovial joint in humans which consists of bony structures (distal femur, proximal tibia, and patella), cartilage (meniscus and hyaline cartilage), ligaments, and a synovial membrane.1-3 The high use and stress on the knee cause osteoarthritis (OA) to occur frequently.1 OA is a chronic condition causing pain, fatigue, functional limitations, increased utilization of health services and high costs for society.4 OA is a progressive and degenerative condition; thus, regression and restoration of damaged structures are impossible.4-5 The goals of OA treatment are to control pain and improve functionality and quality of life.1,4 Non-pharmacological treatments should always be tried as the first line, but the success rate is minimal.1,4,5 Symptomatic therapy such as paracetamol and non-steroidal anti-inflammatory drugs (NSAID) can cause gastrointestinal, renal, cardiac, and hematological side effects with long-term use.1 Conservative treatments such as intra-articular (IA) corticosteroids have limited safety because they are partially absorbed systemically, possibly causing hypoglycemia and interfering with the hypothalamic-pituitary-adrenal (HPA) axis in 25% of patients.1 Hyaluronic acid may be more effective in patients with more severe knee pain, younger age, and lower Kellgren and Lawrence (KL) scores.4 Autologous conditioned serum (ACS), platelet-rich plasma (PRP), and mesenchymal stem cell (MSC). IA reduces cytokine-mediated inflammatory reactions, anabolism induction, and chondrocyte differentiation. This method is promising and well-tolerated but has safety limits, so further research is needed.1 Joint replacement surgery is effective, but it is expensive and has postoperative risks. Therefore, safe and effective non-surgical therapy is still a priority.5

Prolotherapy ("proliferative therapy" or sclerotherapy) is a non-surgical injection therapy used to treat chronic pain in musculoskeletal conditions, including knee OA.5-8 Prolotherapy is a new alternative to TKR.9 Prolotherapy is performed by injecting an irritant into the joint, ligament or tendon gap.8,9 Dextrose (hypertonic dextrose prolotherapy/HDP) is the agent of choice at present.6 NSAID, PRP, and botulinum toxin type A can be used but are less effective.9 This solution creates local irritation, inflammation, and tissue regeneration, thereby increasing the strength of damaged ligaments, tendons, and intra-articular structures.8 The effects
are beneficial in the short, medium and long terms. There are no side effects, and the price is more affordable.\textsuperscript{7} The prolotherapy protocol for OA is by injection of a dextrose solution with a concentration of 12.5\% to 25\% intraarticularly.\textsuperscript{8}

This case series aims to report the effect of hypertonic dextrose prolotherapy on 3 subjects with knee OA at the Physical Medicine and Rehabilitation Polyclinic of dr. Ramelan Navy Hospital Surabaya. We assess the changes in complaints, functionals, and plain radiographs of the subjects after prolotherapy using VAS and WOMAC scores, as well as radiological evaluation.

METHOD

This research was conducted in accordance with ethical principles. Patients who met the inclusion criteria and were willing to be research subjects had signed the informed consent.

This experimental case series was done from December 2021 to April 2022. The research subjects were 3 patients diagnosed with any Kellgren and Lawrence grades of knee OA at the Physical Medicine and Rehabilitation Polyclinic of the dr. Ramelan Navy Hospital Surabaya who were willing to participate in this research, 50 years old and more, have been diagnosed with knee OA based on clinical and radiographic according to the ACR definitions and VAS \( \geq 5 \) despite being treated with regular modalities such as Diathermy, TENS, as well as strengthening and stretching exercises of quadriceps muscles for at least 16 times. Patients who refused to participate in this research had undergone knee joint replacement surgery, were pregnant, receiving anticoagulant therapy, or were diagnosed with other arthritis, as well as patients with allergies or hypersensitivity to the regimen that was going to be given were excluded.

Subjects were not allowed to take pain medication for 3 days before the procedure. Each subject was in a supine position, then hypertonic dextrose prolotherapy (HDP) 25\% (a mixture of 3 cc of 40\% dextrose, 3 ml of Water for Injection, and 1 ml of Lidocaine) was injected slowly into the OA knee using a 22G or 23G needle intraarticularly. After the injection, each patient was advised to apply a cold compress to the painful area. The injection was performed 3 times on each subject, with an interval of 4 weeks each. Each subject still received routine modalities of Diathermy and TENS, as well as strengthening and stretching exercises of quadriceps muscles. All prolotherapy injections were performed by the same doctor.

The assessment of VAS (Visual Analogue Scale) and WOMAC (Western Ontario and McMaster Universities Arthritis Index) scores, as well as the 2\textsuperscript{nd} knee plain radiograph, were carried out 1 month after the 3\textsuperscript{rd} injection for our evaluation. Pain intensity was assessed by VAS, which is a horizontal line of 100 mm long. The assessment was self-administered by each patient and should be completed within a minute. The numerical value on the VAS was obtained as the distance from “no pain” to the point marked on the line by the patient; no pain (0-4 mm), mild (5-44 mm), moderate (45-74 mm), and severe pain (75-100 mm).\textsuperscript{10} Each patient also filled out the WOMAC questionnaire consisting of 3 components, namely pain (a total of 20 points), stiffness (a total of 8 points), and physical function (a total of 68 points). Each question will be rated by the patient; no pain (0-4 mm), mild pain (0-24), moderate (25-48), severe (49-72), and very heavy (73-96). It should be done by the patients within 5-10 minutes, based on their complaints in the last 48 hours. A high score indicates severe symptoms and poor functioning.\textsuperscript{10,11}

The knee joint space width (JSW) measured on AP/PA knee radiographs is an indirect measurement of cartilage width. It is the only imaging biomarker recommended by the United States Food and Drug Administration (FDA) as a structural endpoint in clinical trials of knee OA. Although MRI is currently recommended for the assessment of cartilage morphology, the high availability and low cost of radiography make JSW still the gold standard for assessing the development of OA.\textsuperscript{12}

CASE 1

A man, 54 years old, Javanese, Indonesian citizen, came with a chief complaint of pain in both knees since 1 year before and getting worse for the last 5 months. Pain in the right knee was more severe, especially when kneeling, squatting, and climbing stairs. The patient couldn’t walk far because of the pain. He also felt stiffness for more than 30 minutes, especially in the morning. The patient had controlled hypertension and diabetes mellitus in the last 1 year. The patient is a retired military officer. Currently, he is only doing mild daily activities at home.

His weight was 65 kg, and his height was 171 cm (BMI 22.3 kg/m\(^2\)). His VAS
was 7-8 when climbing stairs, squatting, and kneeling, and decreased to 5-6 when resting. On the physical examination, varus, crepitus, and positive patellar grind test were found. His WOMAC score was 51.

His uric acid, blood sugar 2 hours after meals, and triglycerides in the laboratory results were increased and then became normal again after taking medicines. The rheumatoid factor was negative. The plain radiological examination revealed grade 2 OA in his right knee (Figure 1) with JSW at medial ± 0.40 cm and lateral ± 0.35 cm in the extended position.

He had received pain and inflammation drugs (meloxicam, eperisone, methylprednisolone) for his knee pain. He also received routine modalities, such as MWD, TENS, and stretching exercises of quadriceps muscles 2 times/week for the last 2 months, but the pain persisted (VAS 6-7).

Intra-articular injection of hypertonic dextrose prolotherapy (HDP) 25% was administered to his right knee 3 times at an interval of 4 weeks each. One month after the 3rd injection, the VAS improved to 3-4 during activity, and the WOMAC score decreased to 42. The plain radiograph of the right knee after injection showed medial JSW ± 0.35 cm and lateral ± 0.30 cm in the extended position (Figure 2).

**CASE 2**

A woman, 71 years old, Javanese, Indonesian citizen, came with chief complaints of pain in both knees 2 years ago, which had worsened in the last 1 year. Pain in the left knee was more severe, especially when kneeling, squatting, climbing stairs, and walking too far. She felt stiffness in both knees for more than 30 minutes, especially in the morning.

The patient has had a history of controlled diabetes mellitus for the last 30 years. She is a retired military officer. Currently, she is doing only mild daily activities.

The patient’s weight was 55 kg, and her height was 158 cm (BMI 22 kg/m²). Her VAS was 7-8 when climbing stairs, kneeling, and squatting; her VAS was 5-6 when resting. On physical examination, the presence of varus, crepitus, and a positive patellar grind test was seen. The WOMAC score was 57.

Her last laboratory results were all within normal limits. The plain radiological examination revealed grade 2 OA in the left knee (Figure 3) with JSW medial ± 0.20 cm and lateral ± 0.30 cm in the extended position.

She had received NSAID peroral for the knee pain. She also received routine modalities of MWD, TENS, and quadriceps muscle strengthening and stretching exercises 2 times/week for the last 3 months. However, the pain still persists (VAS 6-7).

An intraarticular injection of 25% HDP was given to her right knee for a total of 3 times at an interval of 4 weeks each. There was an improvement in the pain scale 1 month after the 3rd injection. The VAS became 3-4 during activity, and the WOMAC score decreased to 45. The plain radiograph of her right knee after injection showed medial JSW ± 0.30 cm and lateral ± 0.30 cm in the extended position (Figure 4).

**CASE 3**

A man, 61 years old, Batak ethnic, Indonesian citizen, came with chief complaints of pain in both knees 2.5 years before, which had worsened in the last 1 year. The pain was more severe in the right knee, especially when kneeling, squatting, climbing stairs, and walking too far. The stiffness persisted for more than 30 minutes, especially in the morning.

He has a history of coronary heart disease (post-stenting 4 years ago) and controlled dyslipidemia, hypertension and diabetes mellitus. He is a retired military officer. He is only doing mild daily activities nowadays.

His weight was 90 kg, and his height was 175 cm (BMI 29.4 kg/m²). His VAS was 7-8 when climbing stairs, squatting, and kneeling, and his VAS was 5-6 when resting. On physical examination, varus, crepitus, and positive grinding test were found. The total WOMAC score was 56.

The last laboratory results were all within normal limits. From the radiological examination, grade 2 OA in the right knee was found (Figure 5), with the right knee JSW medial ± 0.35 cm and lateral ± 0.30 cm in the extended position.

He had already taken NSAID for knee pain. He had also received routine modalities, such as MWD, TENS, and quadriceps muscle strengthening and stretching exercises, 2 times/week for the last 3 months. However, he is still suffered from knee pain (VAS 6-7).

Then, we gave an injection of 25% HDP in the right knee for a total of 3 times at an interval of 4 weeks each. There was an improvement in pain 1 month after the 3rd injection: the VAS was improved to 4-5, and the WOMAC score became 43. Plain radiographs of his right knee after injection showed medial JSW ± 0.40 cm and lateral ± 0.35 cm in the extended position (Figure 6).

**DISCUSSION**

The goal of prolotherapy is to create controlled acute inflammation by repeatedly injecting proliferative solutions into chronically problematic areas. Prolotherapy has been shown to be significantly effective in reducing neovascularization which is often correlated with clinical improvement. This proliferative solution can create local irritation, inflammation, and tissue regeneration, thereby increasing the strength of damaged ligaments, tendons and intra-articular structures. Platelets, macrophages and fibroblasts are attracted to the injection site during the...
inflammatory stage. Many growth factors, such as platelet-derived growth factor (PDGF), transforming growth factor (TGF), insulin-like growth factor (IGF), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), and fibroblast growth factor (FGF) are secreted by platelets, macrophages, and fibroblasts for the healing process.8 Hyperosmotic shock induces activation and translocation of glucose transporters (GLUT1 and GLUT4) in mammalian cells. Other studies have shown that GLUT1 can be activated in glucose-deficient fibroblasts.4 Treatment with hyperosmotic dextrose stimulates cell death through the induction of apoptosis and also reduces cell proliferation. Dextrose increases angiogenesis and apoptosis through the VEGF, PDGF, IGF, CASP3 and CASP8 genes, causing wound healing in prolotherapy.8 In the application of high-dose dextrose concentrations, local cell death can lead to increased stimulation which is responsible for the healing process regulation. Regular apoptotic changes and cell death were seen in fibroblast cells treated with high concentrations of dextrose. Cell morphology changes in cell viability analysis assays, and the ratio of cell proliferation and cell viability is reduced.8 HDP is more effective than infiltration with local anesthetics, as effective as HA, ozone or radiofrequency, but less effective than platelet-rich plasma (PRP) and erythropoietin.7

The protocol for using HDP for knee OA is by injection of 12.5% to 25% dextrose solution intraarticularly.6 Treatment was administered at 2 to 4-month intervals.6 All patients were asked to avoid other injection therapies during the research.13 All injections were administered by the same physician. In these 3 patients, prolotherapy was administered with a mixture of 3 ml of 40% dextrose, 3 ml of Water for Injection, and 1 cc of Lidocaine HCl as a local anesthetic, 3 times with a 4-week interval each. This research is consistent with Sit et al.5 and Fathoni and Sudibyo13, who also used 1% H.C.L. as a local anesthetic.

When administered accurately, this therapy is safe and causes minimal pain. After the procedure, the patient may experience pain due to the induction of the inflammatory response. The patient is advised to rest the affected tissue and its use or repeated loading. Gentle passive or active assistive movements are recommended. Patients should stop taking NSAIDs for 2 to 3 days before the procedure to allow the inflammatory response to begin.6 Hemarthrosis and post-injection pain are possible side effects.9 Other studies have found minimal side effects in the treatment and control groups. Mild to moderate pain, inflammation and self-limiting hematoma were reported.7 In all 3 subjects of this research, the side effects were only post-injection pain which disappeared within 1-2 days. This situation is in accordance with a study by Sit et al., Farpour, and Rahimzadeh, who reported that no side effects or adverse reactions occurred.5,14,15

Sit et al. administered 4 injections at weeks 0, 4, 8, and 16 with 5 ml of dextrose solution 25% (mixture of 2.5 ml 50% dextrose and 2.5 ml sterile water)5 in a randomized controlled trial in 76 knee OA patients, showed that HDP IA injection reduced pain, improved function and quality of life in patients with knee OA compared with normal saline injection. The procedure is easy and safe, and compliance and patient satisfaction rates are high.8 Rezasoltani et al.9 compared periarticular and intraarticular injections of prolotherapy in 104 chronic OA patients, who were divided into intraarticular and periarticular groups. They gave injections of 8 ml of 10% dextrose and 2 ml of infra-patellar 2% lidocaine with a G23 needle, which were repeated 1 and 2 weeks after the first injection to the IA group. Whereas in the periarticular group, 5 ml of 1% lidocaine and 5 ml of 20% dextrose were mixed, then 2.5 ml of the solution was injected subcutaneously at 4 points around the knee where the periarticular nerve exits the joint capsule with a 23G needle, and repeated at 1 and 2 weeks after the first injection.9 Fatoni and Sudibyo13 administered hypertonic dextrose injection 25% IA (3.5 ml of dextrose 40% and 2 ml of Lidocaine 2% with a total volume of 5.5 ml) performed 4 times with an interval of 2 weeks, showing improvement in pain scale in chronic knee OA patients post-injection as measured by NRS, from 7 (patient admission) to 4 (post-treatment).13 Arias-Vasquez et al. made a comparison between hypertonic dextrose prolotherapy with different methods and other substances. HDP was found to be more effective in reducing pain, improving tissue function, and beneficial in the long term, and no harmful side effects were found.16 In patients with symptomatic knee OA and anterior cruciate ligament (ACL) weakness, intermittent dextrose injections resulted in an improvement in weakness, pain, swelling, and range of motion (ROM) significantly. Several studies support the use of knee IA injection as an intervention in arthritis.9

Improvements in knee pain, function, and chondrogenesis have been reported in randomized controlled trials (RCTs), systematic reviews and meta-analyses.5,6 However, the independent contribution of IA injection compared to extra-articular is unknown. The extra-articular injection protocol requires special training that is not normally accepted in conventional medical education. These factors may limit patients’ access to prolotherapy.5 Positive effects of a shortened protocol (IA injection only) have been reported, although studies were limited by poor design, small sample size, or lack of control therapy. The primary care provider is well positioned to perform the shortened technique, given that knee IA injection is immediate and safe.5 IA injection is controversial among many clinicians because of the insertion of the needle into the articular capsule and possible side effects.9

The use of hypertonic dextrose prolotherapy in humans can help reduce degenerative processes in cartilage, but few studies have involved radiological follow-up. In this research, the gap between the knee joints with OA was found to be slightly wider after treatment. There was also an improvement in the VAS and WOMAC scores in all 3 patients, indicating a reduction in pain and functional improvement. This research is in agreement with Rabago et al.,17 as well as Hauser and Woldin.18 Clinical trial studies by Rabago et al.16 showed knee OA patients who received 3 times of prolotherapy injections with 10% dextrose, Lidocaine, and bacteriostatic water after 12 months. Radiological results showed the gap between the
joints decreased and the thickness of the cartilage increased. A study by Hauser and Woldin\(^{18}\) with dextrose and Bone Marrow prolotherapy showed an increase in joint space width on plain radiographs of the knee in OA patients after treatment, indicating articular cartilage regeneration. This improvement also coincided with improvements in function and pain levels.\(^{17}\) The study conducted by El-Dosoky et al. showed that there was no significant difference in plain radiographs of the knee joint before and 6 months after prolotherapy, and it was recommended to repeat it after 1 year.\(^ {19}\) Therefore, further large-scale clinical trial research is still needed.

However, there are some limitations to this research. In this research, we just enrolled 4 OA patients, all of whom were injected with HDP IA only. We didn’t compare this procedure with other methods of prolotherapy, or other injection therapies, such as PRP, Hyaluronic Acid, or Steroids that can be used for knee OA. Thus, we can’t report a strong clinical effect from HDP IA and its superiority over other procedures. For the evaluation after the procedures, we only took the plain radiograph, which is cheaper and fast but has less superiority than USG and MRI. Here, we also didn’t do statistical analysis. Further research with USG or MRI evaluation, larger samples, and RCT design with statistical analysis is still needed.

CONCLUSION

In all 3 subjects with knee OA, the knee JSW was slightly widened after treatment. There was also improvement inVAS and WOMAC scores, which indicated a reduction in joint pain and stiffness, as well as functional improvement in all subjects. The hypertonic dextrose prolotherapy in these 3 patients was safe, had minimal side effects (post-injection pain), was affordable price, and was a fast process. Therefore, further large-scale clinical trial research and statistical analysis are still needed.

CONFLICT OF INTEREST

There were no conflicts of interest in this study.

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AUTHOR’S CONTRIBUTION

All authors have made the same contribution in writing the report on the results of this study, from proposal preparation, data search, and data analysis, to interpretation of research data and presentation of the final report.

REFERENCES


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