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Case Report

Periarticular Dextrose Prolotherapy for Patients with Primary Knee Osteoarthritis: A Case Report and Literature Review

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Knee osteoarthritis (OA) is a common disease that primarily afflicts older adults. The mainstream management of knee OA involves integrative practice, including patient education, weight reduction, exercise, pharmacological therapy, and non-pharmacological modalities. However, prolotherapy with hypertonic dextrose via either intra-articular or periarticular injection, or a combination of both techniques, has become a strong evidence-based treatment or adjuvant therapy that may be used in addition to conservative management. In the literature, two studies have compared the effects of intra-articular and periarticular prolotherapy for knee OA and reveal comparable effects. In addition, the periarticular approach has fewer side effects and post-injection pain. Therefore, periarticular prolotherapy may be a favored method given the lower complication rate. We reported on a patient suffering from long-term knee OA in whom conservative treatment had failed. On our suggestion, he received prolotherapy with ultrasound-guided hypertonic dextrose injection over ligament–bone insertions of the medial collateral ligament of the knee for six sessions. After the therapy, both his pain and disability index improved. (Tw J Phys Med Rehabil 2021; 49(2): 213 - 220)

Key Words: prolotherapy, ultrasound,knee osteoarthritis

INTRODUCTION

Osteoarthritis (OA) is a degenerative disease that manifests mainly with painful joints, articular stiffness and decreased function.[1] Although the exact origins of the pain and disability are not clear, various pain generators in the articular capsule, ligaments, synovium, bone, lateral meniscus, and periarticular ligaments and tendons have been implicated.[1] The literature has shown that around 13% of women and 10% of men aged 60 years and older suffer from symptomatic knee OA.[2] Moreover, women are inclined to have more severe knee OA, especially after menopause, and the incidence increases as a result of hormonal changes.[3,4] Knee OA is a degenerative, disabling, and incurable disease, with most patients living with it for decades. Treatment options for knee OA, including lifestyle modification, pharmacol-

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ogical management, and surgical intervention, have been proposed widely and applied extensively.[5,6] Commonly used medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs), may have pain relief effects and provide functional improvement.[7] However, there are gastrointestinal side effects to such medications, and safety concerns should be considered because many aging patients have comorbidities, and thus, they are more vulnerable to these agents.A review by the Agency for Healthcare Research and Quality (AHRC) noted that evidence for several common therapies, including glucosamine, chondroitin, intra-articular viscosupplementation, and arthroscopic lavage, did not demonstrate a clinical benefit.[8] Surgical options are invasive and generally indicated for those refractory to conservative management.[5,6]

Alternative therapies, such as knee injections, can alleviate pain and are less invasive compared with surgery. Among knee injections, prolotherapy has been appealing in the past decade. This therapy was originally termed "sclerotherapy" in the 1800s, and it was used for repairing hernias with irritating injections, based on the concept that it would stimulate tissue repair. In the 1930s, Dr. Earl Gedney expanded the technique by injecting solutions into ligaments, and the result was good.[9] Prolotherapy includes injection at attachments of soft tissue supportive structures, such as ligaments and tendons, and within intra-articular spaces.[10] Because of the purported effects of prolotherapy on degenerative tissue, including revitalization and reorganization, it has also been categorized as a "regenerative" injection therapy by some researchers.[11] A core principle is the injection of small volumes of an irritant solution at multiple painful ligament and tendon insertions and in adjacent joint spaces over several treatment sessions.[12] There are now various injectants, such as saline; hypertonic dextrose, the most common solution; and the more recent platelet rich plasma (PRP).[13] Intra-articular prolotherapy agents can initiate the proliferation and regeneration of damaged cartilage tissue. However, at the same time, the introduction of needles into the articular capsule may cause possible side effects, such as post-injection pain or hemarthrosis. Periarticular prolotherapy involves injections around periarticular sensory nerves, especially their points of fascial penetration where they reach the subcutaneous plane.[1] Here, we report a case of primary knee OA where the patient's pain and disability improved with periarticular dextrose prolotherapy.

CASE REPORT

We present the case of a 60-year-old Taiwanese man with an insignificant medical history who had worked in the building field for more than 40 years. Over the past few years, on and off, he felt pain and stiffness in the medial aspect of his knee when going up and down stairs, and this sensation was worse going down. Six months prior, he had reported to the local clinic with the complaints that he could not get up from a seated to standing position and had difficulty walking and squatting. An X ray performed at the clinic showed the presence of knee OA. The patient started taking NSAIDs and received physical modalities and strengthening exercises for 2 months. He also received an intra-articular steroid injection. However, the symptoms persisted; the visual analog scale (VAS) for pain, measured using a range of 0–10, showed a pain level of 7. Thus, he came to our clinic with an antalgic gait.

Based on the clinical situation, we examined the marked tender medial knee locations and noticed that the left knee was slightly swollen compared with the right, but without erythema or deformity. Range of motion of the left knee was restricted, at 90 degrees of flexion. Patellar tracking deficit, mild crepitus, and tenderness at the medial collateral ligament of the left knee were evident. The anterior drawer test and McMurray's test were negative. We performed musculoskeletal ultrasound and suggested the possibility of undergoing periarticular dextrose prolotherapy.

Figures 1–4 show the X-ray and ultrasound of his left knee performed before injections. For the imaging , the patient was lying supine with slight hip external rotation and knee flexion of 20 degrees. The probe was placed between the medial tibial plateau and the medial femoral condyle in the coronal plane. Hyperechoic osteophytes were found at the medial tibiofemoral joint. The medial collateral ligament was displaced from its original straight course by the osteophytes. The heterogeneously hypoechoic deep meniscofemoral band of the medial collateral ligament was considered abnormal.

Under the aseptic procedure, we performed periarticular injections. To do this, 1 mL of 2% lidocaine, 2 mL of 50% dextrose, and 2 mL of bacteriostatic water were mixed in a syringe, and 5 cc of the solution was injected subcutaneously at four points with a peppering technique around the medial knee where the ligament–bone insertions of the medial collateral ligament were located. One puncture site under ultrasound guidance (Toshiba Aplio 300 Ultrasound System) was allowed for placement of solution at up to four ligament–bone insertions using a skin-sliding technique (withdrawing the needle to just below the skin and reinserting into an adjacent area without removing it from the initial puncture site), allowing for the placement of up to 5 mL of solution. The injection was performed fan-wise with 1.25 mL of drug solution at each point using a 25 G x 1-3/4" hypodermic needle. The patient received periarticular dextrose prolotherapy for about 3 months at intervals of 2 weeks, for a total of six sessions. After the injection, the patient was offered acetaminophen tablets to use as needed for up to 3 days; instructed to avoid hard workouts for 2-3 days but to perform his usual exercisesas long as he did not overstress the knee. He was discouraged from using NSAIDs and from starting new therapies for his OA during the study period.

All injections were performed by the same physician. At each visit, the VAS for pain and the disability index using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score, range of motion, and patient satisfaction were measured. In the WOMAC score, the scale of difficulty for different movements is classified based on the following scale: 0 = none, 1 = slight, 2 = moderate, 3 = very, and 4 = extremely difficult.[1] At the last visit, ultrasonic and radiological assessments were also performed. Finally, the VAS decreased from 7 to 0, and the WOMAC score changed from 4 to 0. The patient reported continued improvement without pain and had already returned to regular exercise after completing six sessions of prolotherapy for 3 months. Due to a health insurance-covered hyaluronic acid injection for knee OA, he did not receive further prolotherapy treatment.

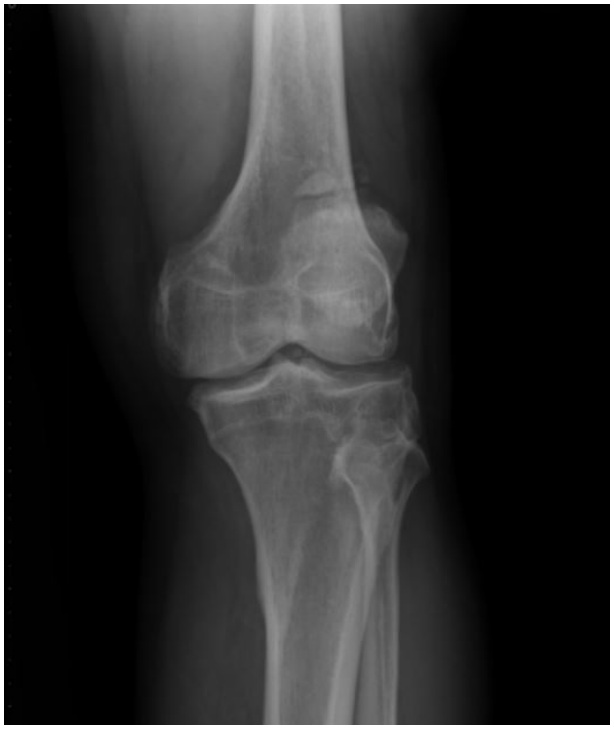

Figure 1. Anterior-posterior projection, left knee X-ray: joint space narrowing with osteophytes, in particular in the medialcompartment.

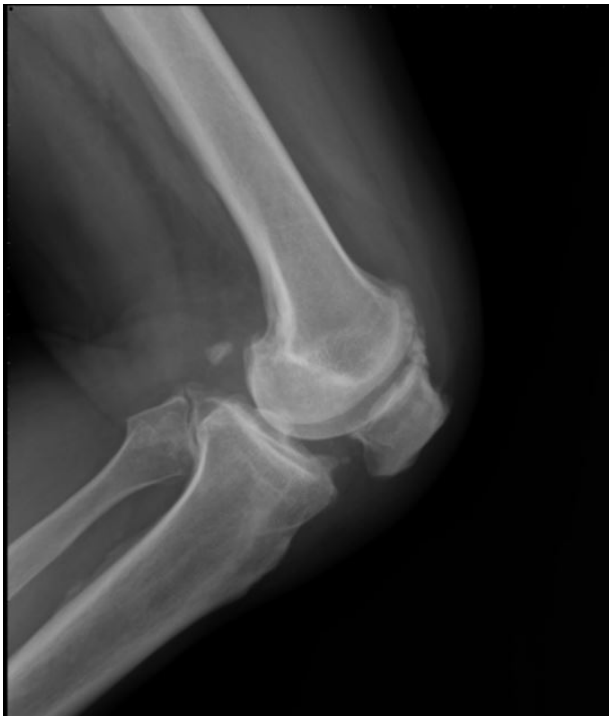

Figure 2. Lateral projection, left knee X-ray: joint space narrowing and fissuring of the patella.

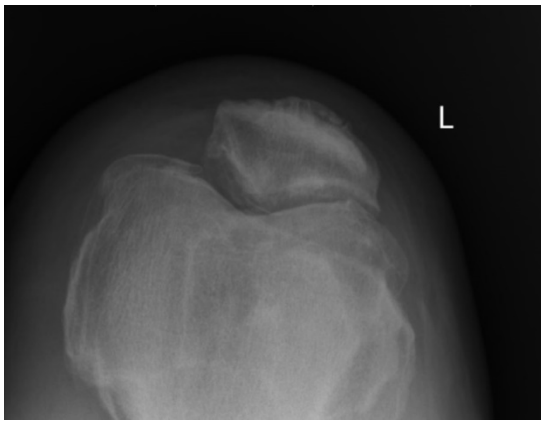

Figure 3. Axial projection, left knee X-ray: lateral tilting of the patella.

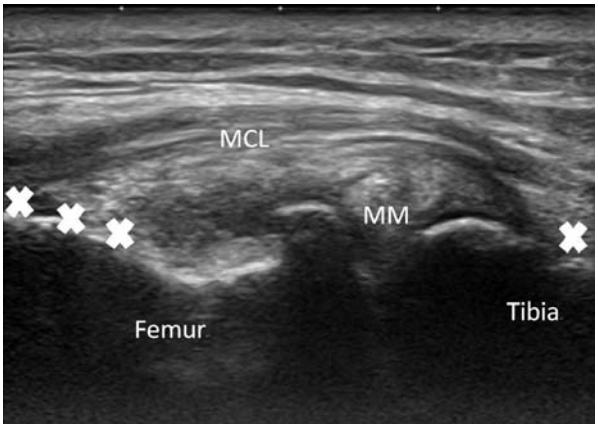

Figure 4. Musculoskeletal ultrasound, left medial knee: Protrusion of the meniscus and osteophytes. (MCL : Medial collateral ligament, MM : Medial meniscus, X : the injection sites)

Table 1. Studies comparing intra-articular verus peri-articular prolotherapy for knee OA. OKS=Oxford Knee Scale

Study	No of participants	Intervention	Injection technique	Outcome measures	Results
Rezasoltani et al. 2017 RCT	104	Intraarticular: 54 Periarticular: 50	Intraarticular: 8 mL of 10% dextrose and 2 mL of 2% lidocaine, with infra-patellar approach by a 23G needle; repeated at 1 and 2 weeks after first injection Periarticular: 5 mL of 20% dextrose mixed with 5 mL of 1% lidocaine; total 2.5 cc of the solution was injected fan-wise with a 23G needle subcutaneously at 4 points around the knee; repeated at 1 and 2 weeks after the first injection	WOMAC VAS	Periarticular prolotherapy injection hascom-parable effects on pain and disabil-ity, and with complication avoidance
Farpour et al. 2017 clinical trial report	52	Intraarticular: 26 Periarticular: 26	Intraarticular: 6 mL of 25% dextrose, with infer-olateral approach by a 25G needle; repeated at 2 weeks after the first injection Periarticular: 6 mL of 25% dextrose at tender points with fan shape technique by a 25G needle; repeated at 2 weeks after the first injection	OKS WOMAC VAS	Both groups improve in VAS, OKS, and WOMAC scores, without any superiority between two groups

WOMAC=Western Ontario and McMaster Universities Arthritis Index, VAS= Visual Analog Scale, OKS=Oxford Knee Scale

DISCUSSION

Prolotherapy, as an interventional medicine for pain management by means of a minimally invasive approach, was first introduced in the 1950s, and it has been adopted

extensively in the present decade. Prolotherapy commonly consists of multiple injection sessions conducted every 2–6 weeks over the course of several months.[10] Hypertonic dextrose (15-25%) is the most common solution, and it is injected at sites of tender ligament and tendon attachments and in adjacent joint spaces.[12] Although the exact mechanism of prolotherapy has yet to be clarified, it is proposed that the proliferant solutions, injected either into the joint space or adjacent ligaments or tendons, cause local tissue irritation and inflammation, with subsequent fibroblast proliferation, growth factor production, and resultant tissue repair, ultimately leading to palliation of pain. Animal model studies have reported increased inflammatory markers, and injured rat medial collateral ligaments injected with dextrose had a larger cross-sectional area compared with both non-injured and injured saline-injected controls.[14]

Another suggested mechanism for periarticular prolotherapy is based on treatment of neurogenic inflammation and neuronal damage related to fiber C transmission of deep pain signals from the knee joint, ligaments, and tendons.[1,15] Injected dextrose may act on relevant pain receptors to reduce neurogenic inflammation and decrease subsequent pain. Animal model and limited human trial data suggest an inflammatory response with direct tissue effects and possible neural effects.[10] Probably, hypertonic dextrose prolotherapy provides both a short-term analgesic effect based on neurogenic mechanisms and a long-term analgesic effect via the repair of soft tissues and cartilage.[16] In addition to dextrose-specific effects, needle trauma and volume expansion of local tissue may also produce tissue-level effects.[17]

Patients who are refractory to conservative management, including non-pharmacological or pharmacological therapy, as well as hesitant to undergo surgical intervention for knee OA, could benefit from the effectiveness of prolotherapy. However, there are a few absolute contraindications to prolotherapy, including acute localized infections, acute gouty arthritis, acute fracture, and acute flare of rheumatoid arthritis.[10] Early in 2000, Reeves et al. first conducted a randomized controlled trial of 10% dextrose prolotherapy for knee OA, and the results showed improvements in pain and function, as well as radiographic results.[18] Several studies have evaluated the effectiveness of prolotherapy for knee OA in the last two decades, where outcome measures, including pain reduction, functional improvement, range of motion, or WOMAC, as well as prolotherapy with hypertonic dextrose for knee OA, have been shown to be effective and safe.[18-20] A systemic review and meta-analysis by Sit RW et al. in 2016 revealed level I evidence of dextrose prolotherapy for knee OA.[21] Case series studies show that hypertonic dextrose prolotherapy application in patients with knee OA promotes pain reduction and improves function for approximately 12 months or longer.[22] It should be noted that the effects could last for a longer time than the effects produced by local anesthetics, corticosteroids, or hyaluronic acid.[16,23] Recent studies reported a similar reduction in pain and function improvement when comparing intra-articular hypertrophic dextrose versus subcutaneous dextrose; this therapeutic effect cannot be attributed to chondrogenic mechanisms or to ligamentous or tendinous remodeling, but perhaps it occurs due to neurogenic effects.[1,14] At the same time, intra-articular injections or puncturing of the joint capsule may cause hemarthrosis and risk of infection. The periarticular method avoids capsular injection and provides an additional modality for pain management in knee OA.[1]

Needle effects include pain, mild bleeding, and a sense of fullness and numbness around the injection site. Such side effects are typically self-limited. A mild to moderate post-procedural pain flare occurs in approximately 10% of patients and may last 1–5 days.[12] NSAIDs are generally avoided because of their potential inhibition of the inflammatory and healing cascade.[10] Regular activities can be progressively resumed over the course of 1-2 weeks after the procedure.

In our case, the patient received periarticular injections at ligament-bone insertions of the medial collateral ligament, which were performed via the peppering technique at four points. A total of six sessionswere conducted at intervals of 2 weeks for 3 months. The patient had progressive improvement on the WOMAC scale, VAS score, and functions that supported returning to regular exercise. However, it should be noted that the VAS and WOMAC scores are subjective scales that depend on individual perceptions, which could be a limitation of our study. There have been studies assessing

intra-articular versus periarticular prolotherapy for knee OA (Table 1), and comparable effects are noted not only on pain but functional improvement. In addition, periarticular prolotherapy could have fewer side effects and complication rates.[1,24]

With the increasingly popular utilization of ultrasound, either intra-articular or periarticular prolotherapy can be performed more accurately and specifically.[25] In addition, we could also avoid vascular puncture or injection with real-time identification of vessels via color Doppler mode. As for safety and cost effectiveness, ultrasound provides low cost and good patient tolerability, while it involves no radiation concern.

CONCLUSION

There is a multidisciplinary approach for the management of knee OA, including pharmacological therapy, lifestyle modification, exercise training, surgical intervention, and alternative options like prolotherapy. Hypertonic dextrose prolotherapy is a safe and evidence-based procedure for knee OA and provides a sustained beneficial effect on the amelioration of pain and functional improvement. Periarticular prolotherapy should be considered the candidate for patients with symptomatic knee OA who are refractory to conservative treatment and hesitant about surgery.

CONSET

Written informed consent was obtained from the patient for publication of this Case Report. A copy of the written consent is available for review by the Editor of this journal.

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關節周圍葡萄糖增生療法治療原發性膝骨關節炎：病例報告及文獻回顧

何彥柔 [1,2]　陳耀仁 [1,2]　何啓中 [1,2]　曾聖維 [1,2]　蔡素如 [1,2]　戴龍偉 [1,2]

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膝骨關節炎是一種相當常見的疾病，主要受影響的是老年人。而目前針對膝骨關節炎的治療仍舊以綜合療法爲主流，包括患者教育、減輕體重、運動訓練，藥物治療及非藥物治療方式。近年來，關節內或關節周圍高濃度葡萄糖增生療法已有強烈證據顯示其療效，也可作爲保守治療的輔助療法；或者同時合併兩種方式也可達到很好的治療效果。

我們報導的這位個案長期受膝關節炎所苦，接受過保守治療一段時間但是仍成效不彰。根據我們的建議，他接受了高濃度葡萄糖增生療法，我們在超音波導引下將高濃度葡萄糖注射到內側副韌帶的韌帶-骨接合處，總共進行了六個療程。治療後，他的疼痛和殘疾指數均有所改善。

在文獻回顧裡，比較了針對膝骨關節炎做關節內與關節周圍增生療法兩種注射方式的效果，結果顯示兩者效果不相上下；而關節周圍注射的額外好處是可以減少副作用與注射後的疼痛感，或許對膝關節炎患者而言是個更佳的選擇。（台灣復健醫誌 2021；49(2)：213 - 220）

關鍵詞：增生療法(prolotherapy)，超音波(ultrasound)，膝骨關節炎(knee osteoarthritis)

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