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Prolotherapy: A nontraditional approach to knee osteoarthritis

Dextrose injections into the knee can reduce pain and improve a patient's quality of life.

PRACTICE CHANGER

Recommend prolotherapy for patients with knee osteoarthritis (OA) that does not respond to conventional therapies.¹

STRENGTH OF RECOMMENDATION

B: Based on a 3-arm, blinded, randomized controlled trial (RCT).

Rabago D, Patterson JJ, Mundt M, et al. Dextrose prolotherapy for knee osteoarthritis: a randomized controlled trial. *Ann Fam Med.* 2013;11:229-237.

ILLUSTRATIVE CASE

A 59-year-old woman with OA comes to your office with chronic knee pain. She has tried acetaminophen, ibuprofen, intra-articular corticosteroid injections, and physical therapy without significant improvement in pain or functioning. She wants to avoid daily medications or surgery and wonders if there are any interventions that will not lead to prolonged time away from work. What would you consider?

Additional options needed for knee OA

More than 25% of adults ages 55 years and older suffer from knee pain, and OA is an increasingly common cause.² Knee pain is a major source of morbidity in the United States; it limits patients' activities and increases comorbidities such as depression and obesity.

Conventional outpatient treatments for knee pain range from acetaminophen, non-steroidal anti-inflammatory drugs, glucosamine, chondroitin, and opiates to topical capsaicin therapy, intra-articular hyaluronic

acid, and corticosteroid injections. Cost, efficacy, and safety limit these therapies.³

Prolotherapy is another option used to treat musculoskeletal pain. It involves repeatedly injecting a sclerosing solution (usually dextrose) into the sites of chronic musculoskeletal pain.⁴ The mechanism of action is thought to be the result of local tissue irritation stimulating inflammatory pathways, which leads to the release of growth factors and subsequent healing.^{4,5} Previous studies evaluating the usefulness of prolotherapy have lacked methodological rigor, have not been randomized adequately, or have lacked a placebo comparison.⁶⁻⁹

STUDY SUMMARY

Prolotherapy reduces pain more than exercise or placebo

Rabago et al¹ randomized 90 participants to dextrose prolotherapy, placebo saline injections, or at-home exercise. Participants had a ≥ 3 month history of painful knee OA based on a self-reported pain scale, radiographic evidence of knee OA within the past 5 years, and tenderness of ≥ 1 or more anterior knee structures on exam.

Sixty-six percent of participants were female. The mean age was 56.7 years and 74% were overweight (body mass index [BMI], 25-29.9) or obese (BMI ≥ 30). Participants chose to have one or both knees treated; 43 knees were injected in the dextrose group, 41 received saline injections, and 47 were assessed in the exercise group. There were no significant differences among groups at baseline.

Participants in the prolotherapy and saline groups received injections at 1, 5, and 9 weeks, plus optional injections at 13 and 17 weeks per physician and participant preference. Injections were administered both extra- and intra-articularly. Intra-articular injections were delivered using a 25-gauge needle with a mixture of 25% dextrose, 1% saline, and 1% lidocaine for a total volume of 6 mL. Extra-articular injections were delivered with a peppering technique with a maximum of 15 punctures over painful ligaments and tendons around the knee. The extra-articular solution was similar to the intra-articular except 15% dextrose was used, with a total maximum volume of 22.5 mL.

The placebo injection group received injections in the same pattern and technique, but the solution was the same quantity of 1% lidocaine plus 1% saline to achieve the same volume. The injector, outcome assessor, primary investigator, and participants were blinded to injection group.

In the exercise group, a study coordinator taught participants knee exercises and gave them a pamphlet with 10 exercises to perform at home. Adherence to at-home exercises was assessed with monthly logs that participants mailed in for the first 20 weeks of the study. Seventy-seven percent of participants reported doing their at-home exercises.

The primary outcome measure was change in composite score on the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC), a validated questionnaire used to evaluate knee-related quality of life that features subscales for pain, stiffness, and function.¹⁰ The minimal clinically important difference in change in score on this 100-point instrument is 12 points; higher scores indicate better quality of life.¹¹ The secondary outcome was change in score on the Knee Pain Scale (KPS), a validated questionnaire that uses a 4-point scale to measure pain frequency and a 5-point scale to measure pain severity; higher scores indicate worse symptoms.¹²

Improvements seen in both scores

Using an intention-to-treat analysis for all groups, WOMAC composite scores improved at 9 weeks and remained improved through 52 weeks. At 9 weeks, the dextrose

group increased 13.91 points, compared with 6.75 ($P=.020$) in the saline group and 2.51 ($P=.001$) points in the exercise group. At 52 weeks, the dextrose group showed an improvement of 15.32 points compared with 7.59 ($P=.022$) in the saline group and 8.24 ($P=.034$) in the exercise group. Fifty percent (15/30) of participants in the dextrose group had clinically meaningful improvement as measured by an increase of ≥ 12 points on the WOMAC, compared with 34% (10/29) and 26% (8/31) in the saline and exercise groups, respectively.

At 52 weeks, the dextrose group had significantly decreased KPS knee pain frequency scores compared with the saline group (mean difference [MD], -1.20 vs. -0.60; $P<.05$) and exercise group (MD, -1.20 vs. -0.40; $P<.05$). Knee pain severity scores also decreased in the dextrose group compared to the saline (MD, -0.92 vs. -0.32, $P<.05$) and exercise groups (MD, -0.92 vs. -0.11; $P<.05$). There were no significant differences in KPS score decreases between the saline and exercise groups.

What about patient satisfaction?

At week 52, all participants were asked, "Would you recommend the therapy you received in this study to others with knee OA like yours?" Ninety-one percent of the dextrose group, 82% of the saline group, and 89% of the exercise group answered "Yes."

All participants who received injections reported mild to moderate post-injection pain. Five participants in the saline group and 3 in the dextrose group experienced bruising. No other side effects or adverse events were documented. According to daily logs of medication use in the 7 days after injection, 74% of patients in the dextrose group used acetaminophen and 47% used oxycodone, compared with 63% and 43%, respectively, in the saline group. The study authors did not comment on the significance of these differences.

WHAT'S NEW

A randomized study provides support for prolotherapy

This study is the first to adequately demonstrate improvement in knee-related quality of life with prolotherapy compared with placebo (saline) or exercise. Family physicians

> Prolotherapy for knee OA reduced pain frequency and severity more effectively than exercise or saline injections.

➤ Prolotherapy for knee OA can be performed in an outpatient setting in <15 minutes; the challenge is finding a certified prolotherapist to do it.

can now add this therapy to their “toolbox” for patient complaints of OA pain.

CAVEATS

Efficacy is unknown in patients with certain comorbidities

Of 894 people screened, only 118 met initial eligibility criteria. This study did not include patients who were taking daily opioids, had diabetes, or had a BMI >40, so its results may not be generalizable to such patients.

Also, while the study demonstrated no side effects or adverse events other than bruising in 8 patients, the sample size may have been too small to detect less common adverse events. However, prior studies of prolotherapy have not revealed any substantial adverse effects.⁷

■ **Strong evidence for some conditions...not for others.** The strongest data support the efficacy of prolotherapy for focal tendinopathy (lateral epicondylitis) and knee OA. Evidence supporting prolotherapy for multimodal conditions, such as chronic low back pain, is less robust.⁴

CHALLENGES TO IMPLEMENTATION

Finding a prolotherapist near you may not be easy

The main challenge to implementation is finding a certified prolotherapist, or obtain-

ing training in the technique. The prolotherapy knee protocol can be performed in an outpatient setting in less than 15 minutes, but the technique requires training. Prolotherapy training is available from multiple organizations, including the American Association of Orthopaedic Medicine, which requires 100 course hours for prolotherapy certification.⁴ No formal survey on the number of prolotherapists in the United States has been conducted since 1993,¹³ but Rabago et al¹ estimated that the number is in the hundreds.

■ **Insurance coverage frequently is a challenge.** Most third-party payers do not cover prolotherapy, and currently most patients pay out-of-pocket. Rabago et al¹ indicated that at their institution, the cost is \$218 per injection session. Another study published in 2010 put the average total cost of 4 to 6 prolotherapy sessions at \$1800.¹⁴

■ **And from the patient’s perspective ...** The multiple needle sticks involved in prolotherapy can be painful. **JFP**

ACKNOWLEDGEMENT

The PURLs Surveillance System was supported in part by Grant Number UL1RR024999 from the National Center for Research Resources, a Clinical Translational Science Award to the University of Chicago. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center of Research Resources or the National Institutes of Health.

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