Prolotherapy describes a procedure intended for healing and strengthening ligaments and tendons by injecting an agent that induces inflammation and stimulates endogenous repair mechanisms. Prolotherapy may also be referred to as proliferant injection, prolo, joint sclerotherapy, regenerative injection therapy, growth factor stimulation injection, or nonsurgical tendon, ligament, and joint reconstruction.

**Background**

The goal of prolotherapy is to promote tissue repair or growth by prompting release of growth factors, such as cytokines, or by increasing the effectiveness of existing circulating growth factors. The mechanism of action is not well understood but may involve local irritation and/or cell lysis. Agents used with prolotherapy have included zinc sulfate, psyllium seed oil, combinations of dextrose; glycerin; and phenol, or dextrose alone, often combined with a local anesthetic. Polidocanol and sodium morrhuate, vascular sclerosants, have also been used to sclerose areas of high intratendinous blood flow associated with tendinopathies. Prolotherapy typically involves multiple injections per session conducted over a series of treatment sessions.

A similar approach involves the injection of autologous platelet-rich plasma (PRP), which contains a high concentration of platelet-derived growth factors. Treatment of musculoskeletal pain conditions (e.g., tendinopathies) with PRP is discussed in policy No 2.01.16.

**Regulatory Status**

The U.S. Food and Drug Administration has approved sclerosing agents for use in treating spider/varicose veins. These sclerosing agents include Asclera® (polidocanol), Varithena® (an injectable polidocanol foam), Sotradecol® (sodium tetradecyl sulfate), Ethamolin® (ethanolamine oleate), and Scleromate® (sodium morrhuate). These agents are not currently approved as joint and ligamentous sclerosing agents.
Prolotherapy is considered investigational as a treatment of musculoskeletal pain.

**Rationale**

Prolotherapy has been investigated as a treatment of various etiologies of musculoskeletal pain, including arthritis, degenerative disc disease, fibromyalgia, tendinitis, and plantar fasciitis. As with any therapy for pain, a placebo effect is anticipated, and thus randomized placebo-controlled trials are necessary to investigate the extent of the placebo effect and to determine whether any improvement with prolotherapy exceeds that associated with a placebo. When this policy was created, there was extensive literature regarding prolotherapy; however, a literature search revealed only 4 randomized placebo-controlled trials. Key studies to date are described below.

### Chronic Neck and Back Pain

In 2004, a Cochrane review concluded that prolotherapy injections have not been proven to be more effective than placebo injections. (1) Two 2005 reviews also noted that there was limited high-quality data to support prolotherapy and that the great variation in injection and treatment protocols limited interpretation of the data. (2, 3) An updated 2007 Cochrane review on prolotherapy for chronic low back pain concluded that “When used alone, prolotherapy is not an effective treatment for chronic low-back pain.” (4) The authors also concluded that, although confounded by cointerventions and heterogeneity of studies, “When combined with spinal manipulation, exercise, and other interventions, prolotherapy may improve chronic low-back pain and disability.” A 2008 systematic review (of the same 5 studies included in the Cochrane review and by one of the same authors) concluded that despite its use for more than 50 years, there is no evidence of efficacy for prolotherapy injections alone for chronic low back pain. (5) The same evidence was evaluated in a 2009 systematic review conducted for the American Pain Society. (6) The authors of this review concluded that prolotherapy was found to be ineffective when used alone for chronic low back pain.

Three randomized trials were identified that focused on the use of injections of dextrose, glycerin, and phenol as a treatment of low back pain. In 1987, Ongley et al. reported on a trial of 81 patients with low back pain who were randomly assigned to receive spinal manipulation plus prolotherapy compared to a control group that received less forceful spinal manipulation, less local anesthesia, and placebo injections of saline. (7) Although improved responses were reported for the treatment group, it is not possible to isolate the possible contribution of the prolotherapy compared to the impact of the different types of spinal manipulation.
In 1993, Klein and colleagues reported on a trial that randomly assigned 79 patients with low back pain to receive a series of 6 weekly injections using either saline or a proliferant solution of dextrose, glycerine, and phenol. (8) Thirty of the 39 patients assigned to the proliferant group achieved a 50% or greater diminution in pain compared to 21 of the 40 in the placebo group. While the incremental benefit of the treatment group was statistically significant (p=0.04), blinding of the treatment groups was not maintained, since those assigned to the proliferant group experienced a clinically recognizable local inflammatory response.

In 2004, Yelland and colleagues reported on a randomized, partially blinded, controlled trial on prolotherapy injections, saline injections, and exercises for chronic low back pain in 110 subjects. (9) While decreases in pain and disability were noted in all study groups, there were no significant differences found between treatment groups at 12 and 24 months. Therefore, the effects of prolotherapy did not significantly exceed placebo effects.

Dagenais and colleagues also conducted a survey of practitioners of prolotherapy for back and neck pain. (10) Completed surveys (n=171, 50% response rate) revealed that practitioners had a median of 10 years of experience, with a median 2,000 treatments in 500 patients. About 500 adverse events (25% of treatments) were reported; 69 (14% of patients) required hospitalization. Adverse events included spinal disc injury, hemorrhage, infection, nerve damage, pneumothorax, spinal headache, spinal cord insult, and systemic reactions. The efficacy of prolotherapy for chronic neck and back pain has not been demonstrated; this procedure is considered investigational.

Osteoarthritis

Rabago et al. reported a randomized controlled trial of prolotherapy for knee osteoarthritis in 2013. (11) This study was supported by the National Center for Complementary and Alternative Medicine (NCCAM). Ninety patients were randomized to blinded injections (3-5 treatments with dextrose prolotherapy or saline) or at-home exercise. All 3 groups showed improvements on the composite Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), with significantly greater improvement in the prolotherapy group (15.3 points) compared to saline and exercise groups (7.6, and 8.2 points, respectively). At 52 weeks, 50% of prolotherapy patients achieved the minimum clinically important difference (MCID) of a 12-point change in WOMAC, compared to 30% of saline-treated patients and 24% of exercise participants. Knee pain scores also improved more in the prolotherapy group. In 2015, Rabago et al reported 2.5-year telephone follow-up from prolotherapy-treated patients in their randomized trial and from 2 uncontrolled open-label studies. (12) The 3 prolotherapy groups were comparable, having undergone similar treatment courses and showing similar improvements in WOMAC score at 52 weeks (15.3, 12.4, 15.9 points, respectively). At a mean 2.5-year follow-up (range, 1.5-3.5 years), the 65 patients who agreed to participate in this follow-up study had a mean 20.9-point improvement in the WOMAC score. There is a risk of bias due to the open-label design and the relatively high proportion (10%) of prolotherapy-treated patients who declined to participate in the telephone interview.

In 2000, Reeves and Hassanein reported on 2 trials that used dextrose for the treatment of osteoarthritis. (13) The first trial randomly assigned 68 patients with 111 osteoarthritic knees to receive either 3 bimonthly injections of dextrose or placebo. The patients were evaluated with a visual analog scale (VAS) for pain and swelling, frequency of leg buckling, goniometrically measured flexion, and
radiographic measures of joint narrowing. As the data are presented, it is clear that there was significant improvement in both the placebo and treatment groups, but it is difficult to determine the comparative magnitude of improvement between the 2 groups. For example, for the various outcome measures of pain, it appears that there are probably no clinically significant incremental effects of prolotherapy compared to the placebo group. However, for other non-pain outcomes, i.e., swelling; buckling; and flexion range, prolotherapy may be associated with a significant incremental improvement. The various outcome measures were combined and assessed using a Hotelling multivariate analysis. With this statistical measurement, prolotherapy demonstrated a statistically superior overall effect (p=0.015) compared to the control group. It should be recognized that the statistical significance of this measure is most likely due to the improvements in the non-pain symptoms (i.e., swelling, buckling, and flexion range). In summary, it is not known whether the incremental improvement in the non-pain-related outcomes of the prolotherapy group compared to the control group is clinically significant.

In a similarly designed study, the same investigators studied the effectiveness of prolotherapy as a treatment of osteoarthritic thumb and finger joints. (14) A total of 27 patients with 150 osteoarthritic joints were randomly assigned to receive 3 bimonthly injections of either dextrose or water. Patients were evaluated with both VAS for pain and goniometric assessment of joint movement. Since patients had a variable number of joints injected (ranging from 1 to 22), the VAS score for every symptomatic joint in each patient was added together for a total and divided by the number of symptomatic joints to provide an average joint pain score for each patient. There were improvements in pain scores in both the placebo and treatment groups, but the incremental improvement of the treatment group compared to the placebo group did not reach statistical significance. In terms of flexion, the treatment group reported a statistically significant improvement (p=0.043), while the placebo group reported a greater, statistically significant decrease (p=0.011). Therefore, the statistically significant difference in flexion between the 2 groups (p=0.003) was primarily related to the decrease in the control group, with a smaller contribution related to the positive response in the treatment group. In summary, the clinical significance of an isolated finding of improved flexion without a corresponding significant improvement in pain is uncertain.

In 2014, Jahangiri et al reported a double-blind randomized trial that compared prolotherapy versus corticosteroid for the treatment of osteoarthritis in the first carpometacarpal joint. (15) Sixty patients were randomized to 3 monthly prolotherapy injections or to 2 monthly saline injections plus a corticosteroid injection in the third month. The groups were comparable at baseline, with a VAS for pain on pressure of 6.7 in the prolotherapy group and 6.4 in the corticosteroid group. At the 6-month follow-up, pain had decreased more (by ≈2 cm VAS; final score, <2) in the prolotherapy group compared with the corticosteroid-treated group (p<0.001). Pain on movement and hand function had also improved to a greater extent in the prolotherapy group.

Tendinopathies of the Upper and Lower Limbs

Lateral Epicondylitis. A 2009 systematic review evaluated injection therapies for lateral epicondylitis (tennis elbow); 2 randomized controlled trials (RCTs) and 1 prospective case series on prolotherapy were included. (16) One of the randomized trials was referenced as a report from a 2006 conference on complementary and alternative medicine; no authors are listed in the reference, and the study does not appear to be available in the peer-reviewed published literature. The second randomized double-
blind placebo-controlled trial involved 20 patients who had elbow pain for at least 6 months and failure of conservative therapy (rest, physical therapy, nonsteroidal anti-inflammatory drugs, and 2 corticosteroid injections) to 3 treatments (over 8 weeks) of prolotherapy or saline injection. There was a significant improvement in pain with prolotherapy injection (from 5.1 to 0.5 on a Likert scale) in comparison with saline injection (4.5 to 3.5). Isometric strength also improved (13 to 31 lb vs. 10 to 11 lb, respectively), but there was no difference in grip strength between the 2 conditions. The authors indicated that this is the first randomized trial of prolotherapy for tendinopathy and that additional research with a larger study population is needed.

A small (17 subjects) randomized double-blind trial of prolotherapy versus corticosteroid injections for chronic lateral epicondylitis was reported in 2011. Each subject received an injection at baseline followed by a second injection at 1 month. VAS for pain, quadruple VAS (QVAS), and Disabilities of the Arm, Shoulder, and Hand questionnaire (DASH) were measured at baseline and at 1, 3, and 6 months. A change of 2 for VAS and 12 for DASH was considered clinically significant. Per protocol analysis showed a significant improvement in VAS and DASH at both 3 (2.38 and 19.89) and 6 months (2.63 and 21.76, both respectively) for the prolotherapy group, while the corticosteroid group showed significant improvement on the DASH at 3 (13.33) and 6 months (15.56). The study was underpowered to detect a significant difference between the prolotherapy and corticosteroid groups for change in VAS, QVAS, or DASH. Larger controlled trials are needed.

Achilles Tendonitis. Yelland et al., an author of Cochrane reviews on this topic, reported a multicenter randomized trial of prolotherapy or exercises for Achilles tendonitis in 43 patients. Inclusion criteria were diagnosis of unilateral or bilateral mid-portion Achilles tendinosis with pain between 2 and 7 cm proximal to the calcaneal attachment in adults older than 18 years with activity-related pain for at least 6 weeks. The sample size was limited by the available resources and slow recruitment rate, resulting in 15 participants in the eccentric loading exercise group, 14 in the prolotherapy group, and 14 in the combined treatment group. Randomization was conducted by a central site and resulted in a lower median duration of pain in the combined treatment group (6 months) than in the exercise alone (21 months) or prolotherapy alone (24 months) groups. An average of 4.4 injections per treatment was directed at tender points in the subcutaneous tissues adjacent to the affected tendon, with 4 to 12 weekly treatments until participants’ attained pain-free activity or requested to cease treatment. The participants were instructed to perform eccentric loading exercises twice daily in 3 sets of 15 repetitions with the knee straight and 3 sets of 15 repetitions with the knee bent for a period of 12 weeks, with the load progressively increased by adding weights to a backpack. Clinical reviews were performed at 3, 6, and 12 weeks to check technique and progress. Mean increases in the validated Victorian Institute of Sport Assessment – Achilles (VISA-A) score were 23.7 for exercise alone, 27.5 for prolotherapy alone, and 41.1 for the combined treatment. At 6 weeks and 12 months, these increases were significantly greater for combined treatment (exercise and prolotherapy) than for exercise alone. The predefined minimum clinically important increase of 20 points or more on the VISA-A was obtained by 12 subjects in the combined treatment group and 11 each in the exercise alone and prolotherapy alone groups. This was not significantly different. The percentage of patients achieving full recovery (VISA-A score of 90 or above at 12 months) was 53% for exercise alone, 71% for prolotherapy alone, and 64% for the combined treatment group, but these differences were not significant. Although the authors concluded that prolotherapy may be a cost-effective method to speed recovery in patients with Achilles tendinosis, this study is limited by the combination of a small number of subjects per group, unequal duration of pain in the treatment groups at baseline, and minimal
differences in the number of patients showing recovery (11 vs. 12, of 14 or 15, respectively). Additional randomized trials are needed to replicate and extend these findings.

Other Musculoskeletal Pain

Reeves and Hassanein reported on a study of dextrose prolotherapy for anterior cruciate ligament (ACL) laxity. (20) Of 16 evaluable patients, statistically significant improvements were found at 6, 12, and 36 months in ACL laxity, pain, swelling, and knee range of motion. However, this was a small, nonrandomized trial and, as noted above, without placebo control, the extent that improvements with prolotherapy exceed those associated with a placebo cannot be determined.

A 2010 publication by Kim et al. compared intra-articular prolotherapy with intra-articular corticosteroid injection for sacroiliac pain. (21) The randomized double-blind study included 48 patients with sacroiliac joint pain lasting equal to or greater than 3 months, confirmed by equal to or greater than 50% improvement in response to local anesthetic block. The injections were performed on a biweekly schedule (maximum of 3 injections) under fluoroscopic guidance with confirmation of the intra-articular location with an arthrogram. Pain and disability scores were assessed at baseline, 2 weeks, and monthly after completion of treatment. At 2 weeks after treatment, all patients met the primary outcome measure of equal to or greater than 50% reduction in pain scores, and there was no significant difference between the 2 groups. The numerical rating scale for pain was reduced from 6.3 to 1.4 in the prolotherapy group and from 6.7 to 1.9 in the steroid group. The Oswestry Disability Index (ODI) decreased from 33.9 to 11.1 in the prolotherapy group and from 35.7 to 15.5 in the steroid group. Kaplan-Meier survival analysis showed a significantly greater percentage of patients with sustained relief following prolotherapy. At 6 months after treatment, 63.6% of patients in the prolotherapy group reported equal to or greater than 50% improvement from baseline in comparison with 27.2% of the steroid group. At 15 months after treatment, 58.7% of patients in the prolotherapy group reported relief equal to or greater than 50% in comparison with 10.2% of the steroid group. Key differences between this and other studies on prolotherapy were the selection of patients using a diagnostic sacroiliac joint block and the use of an arthrogram to confirm the location of the injection. Additional trials are needed to confirm the safety and efficacy of this procedure.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

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<td>NCT01617356</td>
<td>Treatment of Temporomandibular Dysfunction With Hypertonic Dextrose Injection: A Randomized Clinical Trial Efficacy</td>
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<td>Dec 2016</td>
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<tr>
<td>NCT01934868</td>
<td>A Comparison of the Long Term Outcomes of Prolotherapy Versus Interlaminar Epidural Steroid Injections (ESI) for Lumbar Pain Radiating to the Leg</td>
<td>160</td>
<td>May 2017</td>
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Practice Guidelines and Position Statements

The 2011 American College of Occupational and Environmental Medicine guideline on knee disorders states that prolotherapy is not recommended in the treatment of knee disorders. (20)

U.S. Preventive Services Task Force Recommendations:

Use of prolotherapy is not a preventive service.

Summary

The evidence on prolotherapy for patients who have musculoskeletal pain (eg, chronic neck, back pain), tendinopathies of the upper or lower limbs, osteoarthritic pain, includes small randomized trials with inconsistent results. Relevant outcomes are symptoms, functional outcomes, and quality of life. The strongest evidence is for the treatment of osteoarthritis, but the clinical significance of the results is uncertain. The evidence is insufficient to determine the effects of the technology on health outcomes.

Medicare National Coverage

The Coverage Issues Manual (CIM) # 35-13 states that prolotherapy, joint sclerotherapy, and ligamentous injections with sclerosing agents are not covered, noting that the medical effectiveness of these therapies has not been verified by scientifically controlled studies. In 1999, on request for reconsideration of coverage of prolotherapy for treatment for chronic low back pain, Medicare retained its decision for noncoverage of prolotherapy again, citing a lack of scientific evidence on which to base a decision. (21)

References

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Effective Date: January 15, 2016
Subsection: Medicine
Original Policy Date: September 8, 2011
Subject: Prolotherapy
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<td>Update Policy</td>
<td>Policy updated with literature review; references 11 and 16 added; reference 20 updated; policy statement unchanged.</td>
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Keywords
Prolotherapy

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on December 4, 2015 and is effective January 15, 2016.

Signature on File
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