

## Prolotherapy

**Effective:** April 1, 2022

**Next Review:** January 2023

**Last Review:** February 2022

### IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

### DESCRIPTION

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.

### MEDICAL POLICY CRITERIA

Prolotherapy is considered **investigational** as a treatment of any condition, including but not limited to musculoskeletal pain.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

### CROSS REFERENCES

None

### BACKGROUND

Prolotherapy has been investigated as a treatment of various etiologies of pain, including

arthritis, degenerative disc disease, fibromyalgia, tendinitis, and plantar fasciitis. As with any therapy for pain, a placebo effect could be anticipated. Therefore, data from adequately powered, blinded, randomized placebo-controlled trials (RCTs) are required to control for the placebo effect in order to determine whether any treatment effect from prolotherapy exceeds that over placebo. The focus of the following evidence review is on systematic reviews (SRs) and RCTs.

## EVIDENCE SUMMARY

### CHRONIC BACK AND NECK PAIN

#### Systematic Reviews

An updated 2007 Cochrane SR on prolotherapy for chronic low-back pain concluded that “when used alone, prolotherapy is not an effective treatment for chronic low-back pain.”<sup>[1]</sup> The authors also concluded that, although confounded by co-interventions and the heterogeneity of studies, “when combined with spinal manipulation, exercise, and other interventions, prolotherapy may improve chronic low-back pain and disability.”<sup>[2]</sup>

The similar evidence was evaluated in a 2008 and 2009 SR, one of which was conducted for the American Pain Society.<sup>[3]</sup> The authors of this review concluded that prolotherapy was found to be ineffective when used alone for chronic low back pain.

#### Randomized Controlled Trials

Kim (2010) compared intra-articular prolotherapy with intra-articular corticosteroid injection for sacroiliac (SI) joint pain.<sup>[4]</sup> The randomized double-blinded study included 48 patients with SI joint pain of at least three months duration, confirmed by 50% or greater improvement in response to SI joint local anesthetic block. A maximum of three injections were performed on a biweekly schedule under fluoroscopic guidance with confirmation of the intra-articular location with an arthrogram. Pain and disability scores were assessed at baseline, two weeks, and monthly after completion of treatment. At two weeks after treatment, all patients met the primary outcome measure of at least 50% reduction in pain scores, and there was no significant difference between the two 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 six months and 15 months after treatment, 63.6% and 58.7%, respectively, of patients in the prolotherapy group reported at least 50% improvement from baseline in comparison with 27.2% and 10.2%, respectively, 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.

### OSTEOARTHRITIS

#### Systematic Reviews

Wee (2021) published a systematic review and meta-analysis involving 11 RCTs (N=837) that evaluated the use of dextrose prolotherapy in knee osteoarthritis.<sup>[5]</sup> The included studies compared dextrose prolotherapy to other injectates (active or placebo) or interventions in

adults with a knee osteoarthritis diagnosis and included three of the RCTs of prolotherapy in knee osteoarthritis summarized below. The conclusion from the review and analysis identified prolotherapy in knee osteoarthritis to be of potential benefit for pain but the studies are at high risk of bias. Only two of the well-designed studies could be used as an unbiased potential consideration of dextrose prolotherapy in knee osteoarthritis. In general, the review identified that the treatment is safe and may be considered only in patients with limited alternative options.

## Randomized Controlled Trials

Sert (2020) reported on an RCT of prolotherapy in symptomatic knee osteoarthritis refractory to conservative therapy.<sup>[6]</sup> A total of 66 patients between the ages of 40 to 70 years were randomized to dextrose prolotherapy, saline injection, or a control group. Injections were blinded and given at zero, three, and six weeks, while the control group was not blinded. All groups performed an at home exercise program. At 18 weeks, the primary outcome, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale score was significantly improved in all groups, with the change in the prolotherapy group (-7.2 points) showing a significant improvement compared to the saline (-3.5 points;  $p < 0.002$ ) and control groups (-3 points;  $p < 0.001$ ). The WOMAC Total Score and pain VAS scores were also significantly improved in all treatment groups at 18 weeks, with a greater improvement in the prolotherapy group (WOMAC: -36 points and VAS: -6 points) compared to the saline group (WOMAC: -22.5 points,  $p < 0.001$ ; VAS: -2.8 points,  $p < 0.001$ ) and the control group (WOMAC: -9 points,  $p = 0.002$ ; VAS: -2.4 points,  $p < 0.001$ ). Rates of patients achieving a minimum clinically important difference of a 12-point change in the WOMAC score were not reported. There were no significant differences between the prolotherapy and saline groups on changes in Short Form 36 (SF-36) mental or physical component scores at 18 weeks. This study was limited by its small sample size and relatively short follow-up. The majority of the included population was composed of women (85.7 to 90.9% of groups) and adhered to the at home exercise regimen (85 to 87% of groups); both of these factors have been shown to increase benefit of prolotherapy limiting generalizability of the findings to all osteoarthritis patients.

Rabago (2013) reported a RCT of prolotherapy for knee osteoarthritis.<sup>[7]</sup> This study was supported by the National Center for Complementary and Alternative Medicine (NCCAM). Ninety patients were randomized to at-home exercises ( $n = 31$ ), or to 3-5 treatments with blinded injections of either dextrose prolotherapy ( $n = 30$ ) in the treatment group or saline ( $n = 29$ ) in the placebo group. Baseline characteristics were similar between groups except for significantly longer pre-treatment duration of knee pain in the placebo injection group, and significantly more prior physical therapy in the exercise group. All three 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. Limitations of the study methodology included the following: small per-group sample size; generalizability limited due to the numerous exclusion criteria; patients were relatively young; there was a lack of patients with very severe baseline WOMAC scores; and the lack of radiographs for some patients.

Rabago (2015) reported 2.5-year telephone follow-up from prolotherapy-treated patients in

their randomized trial and from two uncontrolled open-label studies.<sup>[8]</sup> The three 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.

Jahangiri (2014) reported a double-blind randomized trial that compared prolotherapy versus corticosteroid for the treatment of osteoarthritis in the first carpometacarpal joint.<sup>[9]</sup> Sixty patients were randomized to three monthly prolotherapy injections or to two 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 six month follow-up, pain had decreased more (by  $\approx 2$  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.

Reeves and Hassanein (2000) reported on two trials that used dextrose alone as a proliferant, thus eliminating the inflammatory response.<sup>[10, 11]</sup> The first trial randomized 68 patients with 111 osteoarthritic knees to receive either three bimonthly injections of dextrose or placebo.<sup>[10]</sup> The patients were evaluated with a visual analogue scale for pain and swelling, frequency of leg buckling, goniometrically measured flexion, and radiographic measures of joint narrowing. As the data were presented, it was clear that there was a significant improvement in both the placebo and treatment groups, but it is difficult to determine the comparative magnitude of improvement between the two groups. For example, for the various outcome measures of pain, it appears that there were probably no clinically significant incremental effects of prolotherapy compared to the placebo group. However, for other non-pain outcomes, e.g., swelling, buckling and flexion range, prolotherapy may be associated with a significant incremental improvement. The various outcome measures were combined as 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 was most likely due to the improvements in the non-pain symptoms. It is not known whether the incremental improvement in the non-pain related outcomes of the prolotherapy group compared to the control group was clinically significant.

In a similarly designed study, the same investigators studied the effectiveness of prolotherapy as a treatment of osteoarthritic thumb and finger joints.<sup>[11]</sup> A total of 27 patients with 150 osteoarthritic joints were randomized to receive three bimonthly injections of either dextrose or water. Patients were evaluated with both visual analogue scale (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 for 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 in 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 two groups ( $p = .003$ ) was primarily related to the decrease in

the control group, with a smaller contribution related to the positive response in the treatment group. The clinical significance of an isolated finding of improved flexion without a corresponding significant improvement in pain is uncertain.

## **TENDINOPATHIES OF THE UPPER AND LOWER LIMBS**

### **Systematic Reviews**

Goh (2021) conducted a systematic review and network meta-analysis of the efficacy of prolotherapy in comparison to other treatments for patients with chronic soft tissue injuries (e.g., tendinopathies and enthesopathies) having a mean symptom duration lasting at least six weeks.<sup>[12]</sup> The review included 91 articles (87 RCTs with 5859 subjects) involving upper limb (74%), lower limb (23%), and truncal/hip (3%) injuries. The "other treatments" within the network meta-analysis were primarily injections such as blood derivatives, corticosteroid, hyaluronic acid, and botulinum toxin. The primary outcome of interest was pain, evaluated mainly at a measurement time point six months post-intervention. If a six month time point was not available then measurements of pain at other times were evaluated. Results revealed that prolotherapy had no statistically significant benefits over other therapies with regard to pain relief at all assessed time points. However, prolotherapy was associated with better pain improvement over placebo at selected time points and injuries, primarily shoulder (<4 and >8 months) and elbow (4 to 8 months) injuries. The authors noted that more than 50% of included studies had a high overall risk of bias and some comparisons were connected by a small number of RCTs.

Chung (2020) published a systematic review and meta-analysis involving 10 RCTs (n=358) that analyzed the effects of dextrose prolotherapy on tendinopathy, fasciopathy, and ligament injuries.<sup>[13]</sup> Included studies compared the effects of hypertonic dextrose prolotherapy to placebo, no prolotherapy, or corticosteroids and evaluated either pain or activity level at follow-up. Results revealed that there were no significant differences between dextrose prolotherapy and no treatment or placebo with regard to pain control for the majority of studies. Dextrose prolotherapy was effective in improving activity only at an immediate follow-up period of zero to one month (standardized mean difference [SMD], 0.98; 95% CI, 0.40 to 1.50) and was superior to steroid injections only in pain reduction at short-term follow-up (1 to 3 months; SMD, 0.70; 95% CI, 0.14 to 1.27). The authors concluded there was insufficient evidence to support the clinical benefits of dextrose prolotherapy in managing dense fibrous tissue injuries.

Three SR analyzed RCTs comparing various peritendinous injections with placebo or non-surgical interventions for tendinopathies.<sup>[14-16]</sup> These reviews reported that, in trials of injections of corticosteroid, sclerosant, platelet-rich plasma, proteinase, glycosaminoglycan polysulfate, sodium hyaluronate, prolotherapy, and botulinum toxin compared with placebo injection or other therapies, only prolotherapy and sodium hyaluronate showed better results than placebo in the short and long term in overall improvement and pain reduction of lateral epicondylitis. These outcomes must be validated in larger, long-term, blinded RCTs.

Gross (2013) conducted a SR of RCTs and comparative cohort studies of various injection therapies for noninsertional Achilles tendinosis.<sup>[17]</sup> Nine studies with 312 Achilles tendons at final follow-up met inclusion criteria. Injectates included platelet-rich plasma (n=54), autologous blood injection (n=40), sclerosing agents (n=72), protease inhibitors (n=26), hemodialysate (n=60), corticosteroids (n=52), and prolotherapy (n=20). The authors designated all studies as having a low quality of evidence with variable results, conflicting methodologies, and inconclusive evidence about indications for treatment and mechanisms of effects. The authors

concluded that treatment recommendations for any injectable therapies for this condition would require additional data collected from RCTs.

## Randomized Controlled Trials

Two RCTs were published in 2020 evaluating the efficacy of dextrose prolotherapy in the treatment of lateral epicondylopathy/epicondylalgia.<sup>[18]</sup> Both of these trials were conducted in Turkey in small patient populations. Akcay (2020) enrolled 60 subjects with chronic lateral epicondylopathy with randomization to dextrose 15% prolotherapy or normal saline injection. Results revealed that there was no significant difference between groups in VAS scores at rest or in motion, Disabilities of the Arm, Shoulder, and Hand (DASH) score, and handgrip strength at any time points in terms of improvement ( $p>.05$ ). Dextrose prolotherapy was noted to outperform normal saline with regard to effect on the Patient Rated Tennis Elbow Evaluation (PRTEE). Additionally, a significant percentage of patients in both groups achieved an MCID for all outcome measurements at the end of 12 weeks with no significant difference among the groups in terms of MCID achievement ( $p>.05$  for VAS at rest and motion, DASH, and PRTEE).

Apaydin (2020) compared the effects of dextrose prolotherapy to hyaluronic acid injection in 32 patients with lateral epicondylalgia.<sup>[19]</sup> Overall, dextrose prolotherapy was favored over hyaluronic acid for improvements in pain with activity, at night, and at rest from baseline to 12 weeks. Dextrose prolotherapy was also associated with a significant improvement in quick-DASH scores. No between-group improvement in grip pain was observed. Results of both studies were limited by a short follow-up time, small sample size, and non-US-based, single center design.

A double-blind RCT reported by Bayat (2019) compared dextrose prolotherapy with corticosteroid injection for chronic lateral epicondylitis.<sup>[20]</sup> Patients ( $n=28$ ) received a single injection during the treatment period. There was a significant improvement in VAS pain score at one and three month follow-up in both the prolotherapy group (mean difference: 1.9 and 4.4 points, respectively) and the corticosteroid group (mean difference: 1.5 and 1.9 points, respectively). No difference was observed between groups in VAS score at one month ( $p=0.74$ ); however, prolotherapy resulted in significantly better scores at three months ( $p=0.03$ ). At one month follow-up, no statistically significant difference was observed between the prolotherapy and corticosteroid groups in the Quick Disabilities of the Arm, Shoulder, and Hand (QuickDASH) score (24.3 vs 34.8, respectively;  $p=0.14$ ); however, Quick DASH score was significantly better with prolotherapy compared to corticosteroid at three months (score=14.7 vs 34.6, respectively;  $p=0.01$ ). Results of this study are limited by a short follow-up, use of a single injection regimen, small sample size, and a notable non-significant difference in baseline symptom duration and QuickDASH score.

Bertrand (2016) reported on an RCT of prolotherapy in rotator cuff tendinopathy with supraspinatus pathology.<sup>[21]</sup> A total of 73 participants were randomized to a blinded injection of dextrose prolotherapy ( $n=27$ ), entheses saline injection ( $n=20$ ), or superficial saline injection ( $n=27$ ), all of which were given at months 0, 1, and 2, along with physical therapy. The primary outcome was achieving at least a 2.8 point improvement on the Numeric Rating Scale (NRS), which was obtained by phone by a blinded evaluator. Because the NRS rates pain in only whole numbers, pain levels are typically rated higher than with the VAS. For this reason, the improvement threshold was set as twice the minimal clinically important difference for VAS change in rotator cuff tendinopathy. After nine months, the primary outcome occurred in 59% of patients in the prolotherapy group, which was significantly higher than in the superficial

saline group (27%;  $p=0.017$ ) and similar to the enthesitis saline group (37%;  $p=0.088$ ). Patient satisfaction at 9 months, assessed using a 10-point satisfaction scale (0=not satisfied, 10=completely satisfied), revealed highest satisfaction in the prolotherapy group (6.7 points), followed by enthesitis saline (4.7 points;  $p=0.079$  compared to prolotherapy) and superficial saline (3.9 points;  $p=0.003$  compared to prolotherapy). Scores from the Ultrasound Shoulder Pathology Rating Scale did not differ significantly between groups ( $p=0.734$ ). Important limitations of this study are the single-center design, which may limit generalizability to all patients. Additionally, the enthesitis saline injection group was not sufficiently powered to find a difference from the prolotherapy group. Finally, the use of the NRS as an alternative to the VAS may have biased the measurement of pain improvement.

One double-blind trial compared the efficacy of prolotherapy with placebo (saline injections) in 20 patients with elbow pain for at least six months and failure of conservative therapy (rest, physical therapy, nonsteroidal anti-inflammatory drugs, and two corticosteroid injections).<sup>[22]</sup> Injections were performed three times over eight weeks. At 16 weeks follow-up there was a significant improvement in pain (from 5.1 to 0.5 on a Likert scale) in the prolotherapy group compared with the placebo group (4.5 to 3.5). Isometric strength also improved (13 to 31lb vs. 10 to 11 lb), but there was no difference in grip strength between the two treatments. The authors indicated that this is the first randomized trial of prolotherapy for tendinopathy; additional research with a larger study population is needed.

Carayannopoulos (2011) randomized 24 patients with lateral epicondylitis of at least three months duration to receive either prolotherapy or corticosteroid injection.<sup>[23]</sup> This was a double-blind study. All subjects received an injection at baseline and a second injection one month later. Both groups reported significant improvement, but there was no significant difference in pain and disability measures between the two groups.

## **OTHER MUSCULOSKELETAL PAIN**

Dextrose prolotherapy has been investigated in temporomandibular joint dysfunction. In 2011, a preliminary randomized, double-blind, placebo-controlled clinical trial was conducted on patients with temporomandibular joint hypermobility.<sup>[24]</sup> Since then, Sit (2021) has performed a systematic review and meta-analysis of five RCTs that compare the efficacy of hypertonic dextrose prolotherapy injections to placebo in patients with temporomandibular joint dysfunction.<sup>[25]</sup>

Current published literature for prolotherapy for other musculoskeletal disorders is limited to preliminary feasibility studies of conditions such as Achilles tendinopathy<sup>[14]</sup>, anterior cruciate ligament laxity<sup>[26]</sup>, osteitis pubis<sup>[27]</sup>, rotator cuff tendinopathy<sup>[28]</sup>, plantar fasciitis<sup>[29]</sup>, and bursitis.<sup>[30]</sup> These studies do not permit conclusions on the efficacy or safety of prolotherapy due to lack of randomization and placebo-control groups, small study populations, and short-term study duration.

## **PRACTICE GUIDELINE SUMMARY**

### **AMERICAN ASSOCIATION OF ORTHOPEDIC MEDICINE**

As of September 2020, the American Association of Orthopedic Medicine (AAOM) currently has a recommendation posted online for the use of prolotherapy for back pain, with an unknown original publication date.<sup>[31]</sup> The AAOM has indicated that "...prolotherapy should be considered a valid treatment option in a selected group of chronic low back pain patients."



## AMERICAN COLLEGE OF RHEUMATOLOGY/ARTHRITIS FOUNDATION

The 2019 American College of Rheumatology/Arthritis Foundation guideline for osteoarthritis of the hand, hip, and knee conditionally recommends against the use of prolotherapy in patients with knee and/or hip osteoarthritis, given limited number of trials involving small sample sizes showing limited effect.<sup>[32]</sup> The guideline does not make any recommendation regarding hand osteoarthritis, given lack of trials.

### SUMMARY

There is not enough research to show that prolotherapy improves health outcomes for people for any indication. Clinical practice guidelines are inconclusive on the use of prolotherapy for the treatment of musculoskeletal pain. Therefore, prolotherapy is considered investigational for all indications, including but not limited to musculoskeletal pain.

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## CODES

Codes	Number	Description
CPT	20999	Unlisted procedure, musculoskeletal system, general
HCPCS	M0076	Prolotherapy

**Date of Origin:** November 1997