Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

Joint Medical Policies are a source for BCBSM and BCN medical policy information only. These documents are not to be used to determine benefits or reimbursement. Please reference the appropriate certificate or contract for benefit information. This policy may be updated and is therefore subject to change.

***Current Policy Effective Date: 9/1/24**
(See policy history boxes for previous effective dates)

Title: Prolotherapy

Description/Background

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.

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, which are vascular sclerosants, have also been used to sclerose areas of high intratendinous blood flow associated with tendonopathies. 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 for treatment of musculoskeletal pain conditions (e.g., tendinopathies) with platelet-rich plasma.

Medical Policy Statement

Prolotherapy is considered experimental/investigational as a treatment of musculoskeletal pain. It has not been scientifically demonstrated to be as safe and effective as conventional treatment.

Inclusionary and Exclusionary Guidelines

N/A

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes

N/A

Other codes (investigational, not medically necessary, etc.)

M0076

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.

PROLOTHERAPY

Clinical Context and Therapy Purpose
The purpose of prolotherapy in individuals who have musculoskeletal pain, osteoarthritic pain, or tendinopathies of the upper or lower limbs is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICOs were used to select literature to inform this review.

Populations
The relevant populations of interest are individuals with musculoskeletal pain, osteoarthritic pain, or upper- or lower-limb tendinopathies.

Interventions
The therapy being considered is prolotherapy.

Comparators
The following therapies and practices are currently being used to treat musculoskeletal pain, osteoarthritic pain, and upper- or lower-limb tendinopathies: observation and other conservative therapies.

Outcomes
The general outcomes of interest are reductions in pain and medication use, improvements in function, and treatment-related adverse events (mostly mild but in rare instances serious).

Varying by condition, injections are administered over a series of sessions, which can last from several weeks to months.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

Chronic Neck and Back Pain

Systematic Reviews
A Cochrane review by Dagenais et al (2007) evaluated prolotherapy for chronic low back pain and concluded that, “When used alone, prolotherapy is not an effective treatment for chronic low-back pain.”(1) Reviewers also concluded that, although confounded by co-interventions and heterogeneity of studies, “When combined with spinal manipulation, exercise, and other interventions, prolotherapy may improve chronic low-back pain and disability.”

Another systematic review by Dagenais et al (2008) of the same 5 studies included in the Cochrane review and by 1 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.(2) The same evidence was evaluated in a systematic review conducted by Chou et al (2009) for the American Pain Society.(3) In this case, reviewers also concluded that prolotherapy was ineffective when used alone to manage chronic low back pain.

Randomized Controlled Trials
Three randomized trials were identified that focused on the use of injections of dextrose, glycerin, and phenol as a treatment of low back pain. Yelland et al (2004) reported on a partially blinded RCT of prolotherapy injections, saline injections, and exercises for chronic low back pain in 110 subjects.(4) While decreases in pain and disability were noted in all study groups, there were no significant differences between treatment groups at 12 and 24 months. Therefore, the effects of prolotherapy did not significantly exceed placebo effects.

Klein et al (1993) reported on a trial that randomly assigned 79 patients with low back pain to receive a series of six weekly injections using either saline or a proliferant solution of dextrose, glycerine, and phenol.(5) 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.

Ongley et al (1987) reported on a trial of 81 patients with low back pain who were randomized to spinal manipulation plus prolotherapy or a control group that received less forceful spinal manipulation, less local anesthesia, and placebo injections of saline.(6) Although improved responses were reported for the treatment group, it was not possible to evaluate the

contribution of prolotherapy compared with the impact of the different types of spinal manipulation.

Other Musculoskeletal Pain

Systematic Review

Bahgat et al (2023) conducted a systematic review of 8 RCTs that evaluated the efficacy of hypertonic dextrose prolotherapy for temporomandibular joint internal derangement.(7) Meta-analysis was not performed, but the authors concluded that dextrose prolotherapy improved joint pain, mandibular deviation, joint sounds, and maximum mouth opening up to 12 months versus comparator therapies. Heterogeneity among studies in dextrose concentration, volume, injection site, and number of injections may limit the generalizability of these findings.

Randomized Controlled Trials

A trail by Kim et al (2010) compared intra-articular prolotherapy with intra-articular corticosteroid injection for sacroiliac pain.(8) The double-blind, randomized study included 48 patients with sacroiliac joint pain lasting 3 months or more, confirmed by 50% or more improvement in response to the local anesthetic block. The injections were performed on a biweekly schedule (maximum of three injections) 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 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 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 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.

Prospective Studies

Reeves and Hassanein (2003) reported on a study of dextrose prolotherapy for anterior cruciate ligament (ACL) laxity.(9) Of 16 evaluable patients, statistically significant improvements were found at 6, 12, and 36 months in anterior cruciate ligament (ACL) laxity, pain, swelling, and knee range of motion. However, this was a small, nonrandomized trial and, as previously noted, without placebo control, the extent that improvements with prolotherapy exceed those associated with a placebo could not be determined.

Osteoarthritis

Systematic Reviews

Waluyo et al (2023) conducted a systematic review of RCTs that compared dextrose prolotherapy to other interventions for osteoarthritis.(10) The 14 included trials represented patients with osteoarthritis of the knee (11 trials), hand (2 trials), hip (1 trial). Nine studies

found that prolotherapy improved functional outcomes more effectively than comparator interventions (e.g., saline, exercise, local corticosteroid injection, hyaluronic acid, pulsed radiofrequency), but 4 trials reported superior efficacy of comparator therapies compared to prolotherapy. For the outcome of pain in generalized osteoarthritis, most studies (n=10) reported that prolotherapy was more effective than comparator interventions. Comparisons with individual treatments found that prolotherapy was more effective than saline and exercise in all included studies. Comparisons with hyaluronic acid, ozone prolotherapy, and autologous conditioned serum yielded conflicting results among studies. Prolotherapy was less effective than platelet-rich plasma in 2 studies. A limitation of this analysis is that most of the studies had a high risk of bias.

Cortez et al (2022) conducted a systematic review involving 8 RCTs (N=660) that compared dextrose prolotherapy with other substances for pain relief (e.g., platelet-rich plasma, exercise programs, hyaluronic acid, saline) in patients with primary knee osteoarthritis.(11) Study size ranged from 42 to 120 patients with gender distribution leaning heavily toward the female sex (61% of the total population). Study assessments ranged from 0 to 52 weeks with the majority of study investigators performing assessments at months 1, 3, and 6. Only 2 studies continued assessments up to the 52 week mark. Dextrose intra-articular injections were primarily applied at weekly or monthly intervals and most studies performed a total of 3 injections. Concentrations of dextrose injections ranged from 12.5% to 25% with 10 mL as the most prevalent volume injected. Overall, patients who underwent dextrose prolotherapy had numerical improvements between baseline and posterior assessments when compared to saline injections regarding pain and function with between-group differences of 7.73 to 14 points on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scale and 1.06 to 3.5 points on visual analogue scale (VAS). However, the results were unclear when comparing dextrose prolotherapy to other substances. The included studies were limited by small sample sizes and the limited time frame for patient assessment. Due to significant heterogeneity of the studies, the intended meta-analysis could not be performed and no conclusions can be drawn based on these findings.

Arias-Vazquez et al (2022) completed a systematic review and meta-analysis involving 6 studies (5 clinical trials and an observational study) of 395 patients with knee osteoarthritis comparing the effectiveness of hypertonic dextrose prolotherapy with intra-articular hyaluronic acid injections on pain reduction and improvement of function.(12) The primary outcomes were pain control (as measured by VAS or the pain subscale score of validated questionnaires) and improvement in function (as measured by scores on validated questionnaires). Both outcomes were assessed at 3 months follow-up. Two hundred patients were treated with hypertonic dextrose prolotherapy and 195 were administered intra-articular hyaluronic acid injections. The groups who received hypertonic dextrose prolotherapy used a solution of hypertonic dextrose combined with local anesthetics, with up to 3 intra-articular injections dependent on study design. For those who received hyaluronic acid, up to 5 intra-articular injections were administered dependent on study design. Pooled results of the clinical trials revealed no significant difference in pain reduction between hypertonic dextrose prolotherapy and hyaluronic acid in the short-term (3 months; p=.06); however, a significant difference in improvement of function was observed in favor of the hypertonic dextrose prolotherapy group (p=.03). No major adverse effects were reported in the 3 studies reporting adverse reactions. Limitations included the small total number of studies, short-term follow-up, unclear or high risk of study bias, and significant data heterogeneity. Better quality clinical trials are necessary to corroborate these results.

Wee et al (2021) published a systematic review and meta-analysis involving 11 RCTs (N=837) that evaluated the use of dextrose prolotherapy in knee osteoarthritis.(13) The included studies compared dextrose prolotherapy to other injectates (active or placebo) or interventions in adults with a knee osteoarthritis diagnosis and included the 3 RCTs of prolotherapy in knee osteoarthritis summarized below (14) Rabago et al (2013;[15]) Reeves and Hassanein (2000; [16]) Study size ranged from 31 to 120 patients. Concentrations of dextrose intra-articular injections ranged from 10% to 25% while extra-articular dextrose injection concentrations ranged from 12.5% to 15%. The number of injections and the intervals between injections were heterogeneous across studies. Overall, the authors concluded that dextrose prolotherapy (as a single 25% intra-articular injection) may confer potential benefits in terms of pain and function for patients with knee osteoarthritis; however, the majority of included studies were at a high risk of bias. The high risk of bias in the included studies was due to deviations from intended interventions and missing outcome data. Many trials did not discuss how missing data or trial deviations were managed and drop-outs were not clearly defined. The blinding of outcome assessors was also not well documented. For the 2 studies that were of low risk, the authors concluded that dextrose prolotherapy may be considered a treatment option in knee osteoarthritis, particularly in patients with limited treatment alternatives; however, despite good study designs, the study interventions were heterogenous across trials. The authors concluded that more high-quality RCTs are warranted to establish the benefits of this intervention.

Randomized Controlled Trials

Bayat et al (2023) reported the results of a randomized, double-blind trial that compared dextrose prolotherapy with intraarticular triamcinolone injection in 50 patients with knee osteoarthritis.(17) Both treatments led to significant improvements in pain (as assessed by VAS and WOMAC) at 1 and 3 months. At month 1, pain control was significantly better with triamcinolone than prolotherapy ($p<.05$). However, at 3 months, both VAS and WOMAC were significantly higher in the prolotherapy group (both $p<.001$). However, the mean differences between groups (e.g., 1.03 to 1.58 points on the VAS) may not have been clinically relevant.

Sert et al (2020) reported on an RCT of prolotherapy in symptomatic knee osteoarthritis refractory to conservative therapy.(14) 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 week 0, 3, and 6, 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.

Jahangiri et al (2014) reported a double-blind randomized trial that compared prolotherapy with corticosteroid for the treatment of osteoarthritis in the first carpometacarpal joint.(18) 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, the 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.

Rabago et al (2013) reported on a randomized controlled trial of prolotherapy for knee osteoarthritis.(15) This trial was supported by the National Center for Complementary and Alternative Medicine (NCCAM). Ninety patients were randomized to blinded injections (3- to 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.(19) The 3 prolotherapy groups were comparable, having undergone similar treatment courses and showing similar improvements in the WOMAC score at 52 weeks (15.3, 12.4, 15.9 points, respectively). At a mean 2.5-year follow-up (range, 1.5 to -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.

Reeves and Hassanein (2000) reported on 2 trials that used dextrose for the treatment of osteoarthritis.(16) The first trial randomly assigned 68 patients with 111 osteoarthritic knees to receive either three 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 presented, the data suggested a significant improvement in both the placebo and treatment groups, but it is difficult to determine the comparative magnitude of improvement between the 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, Reeves and Hassanein (2000) also assessed the effectiveness of prolotherapy as a treatment of osteoarthritic thumb and finger joints.(20) Twenty-seven patients with 150 osteoarthritic joints were randomized to 3 bimonthly injections of 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 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.

Tendinopathies of the Upper and Lower Limbs

Chronic Soft Tissue Injuries

Systematic Reviews

Fong et al (2023) conducted a systematic review and meta-analysis of 8 RCTs that investigated the effect of hypertonic dextrose prolotherapy for plantar fasciopathy.(21) Based on low certainty evidence, prolotherapy resulted in significant pain reductions and improved function compared to saline in the medium term. Prolotherapy was similar to local corticosteroid injections in pain reduction in the short term. The risk of bias varied from some concern to high among the included studies. A similar meta-analysis by Ahadi et al (2023) included 8 RCTs of dextrose prolotherapy for chronic plantar fasciitis.(22) Prolotherapy was better than comparator therapies in reducing pain, improving function, and reducing plantar fascia thickness in the short term. Almost all studies in the analysis had a high risk of bias and long term results were generally not available.

Goh et al (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 6 weeks.(23) 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 6 months post-intervention. If a 6-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 et al (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.(24) 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 0 to 1 month (standardized mean difference [SMD], 0.98; 95% CI, 0.40 to1.50) 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.

Lateral Epicondylitis

Systematic Reviews

Zhu et al (2022) conducted a systematic review and meta-analysis involving 8 parallel or crossover RCTs (N=354) that evaluated the efficacy or effectiveness of dextrose prolotherapy on pain intensity and physical functioning in patients with lateral elbow tendinosis as compared to other active non-surgical treatments.(25) The majority of the included RCTs are summarized below [Scarpone et al (2008; {26}); Akcay et al (2020; {27}); Apaydin et al (2020; {28}); Bayat et al (2019; {29}); Carayannopoulos et al (2011; {30})]. Study sample sizes of the included RCTs ranged from 24 to 120 patients. The study periods ranged from 8 to 52 weeks with an injection frequency of 1 to 4 injections, weekly to 4 weeks apart; dextrose concentrations ranged from 12.5% to 50%. Comparison controls were classified into active (e.g., various injection solutions or therapies such as exercise, shock wave, laser, or manual therapy) or inactive (e.g., no treatment, watchful waiting, bracing) categories. The primary outcome of interest was pain reduction, measured by VAS, numerical rating scale (NRS), or algometry. Secondary outcomes included handgrip strength, the Disabilities of the Arm, Shoulder, and Hand (DASH) score, and the Patient Rated Tennis Elbow Evaluation (PRTEE) score. Pooled results revealed dextrose prolotherapy to be significantly more effective than active controls at reducing pain intensity (p=.04) and improving DASH cumulative score (p<.001) at 12 weeks. However, dextrose prolotherapy had no significant effect on PRTEE cumulative score (p=.70) at 12 weeks or grip strength (p=.90) at 12 to 16 weeks. There were no significant related adverse events of dextrose prolotherapy. The overall quality of evidence ranged from very low to moderate with a high heterogeneity across the RCTs. Additionally, the number of studies included and the total participant sample size were small, the time frame available for pooling data was short (12 to 16 weeks), and quantitative syntheses included only a small number of studies in most comparisons (2, 3, or 4 RCTs).

A systematic review by Rabago et al (2009) evaluated injection therapies for lateral epicondylitis (tennis elbow); 2 randomized controlled trials (RCTs) and a prospective case series on prolotherapy were included.(31) 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) and who received 3 treatments (over 8 weeks) of prolotherapy or saline injection.(26) 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 both groups.

Randomized Controlled Trials

Two RCTs were published in 2020 evaluating the efficacy of dextrose prolotherapy in the treatment of lateral epicondylopathy/epicondylalgia. Both of these trials were conducted in Turkey in small patient populations. Table 1 summarizes key study characteristics and Table 2 presents a summary of results. Akcay et al (2020) enrolled 60 subjects with chronic lateral epicondylopathy with randomization to dextrose 15% prolotherapy or normal saline injection.(27) 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 et al (2020) compared the effects of dextrose prolotherapy to hyaluronic acid injection in 32 patients with lateral epicondylagia.(28) 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 in quick-DASH scores. No between-group improvement in grip pain was observed. Results of both studies were limited by a short follow-uptime, small sample size, and non-US-based, single center design.

Table 1. Summary of RCT Characteristics

Study	Countries	Sites	Participants	Interventions	
				Active	***Comparator***
Akcay et al (2020)	Turkey	1	Adults with chronic lateral epicondylopathy with pain at the lateral side of the elbow lasting a minimum of 3 months despite treatment (N=60)	Dextrose 15% prolotherapy (n=30) injection given at baseline and at the end of the 4th and 8th weeks	Normal saline (n=30) injection given at baseline and at the end of the 4th and 8th weeks
Apaydin et al (2020)	Turkey	1	Adults with a clinical diagnosis of lateral epicondylagia of at least 6 months duration, pain provoked by palpation and resisted wrist/middle finger extension or gripping, and a score of at least 30/100 on the VAS (N=32)	Dextrose 15% prolotherapy (n=16) injection at weeks 0, 3, and 6	Hyaluronic acid (n=16) injection administered as a single 30 mg dose at baseline

RCT: randomized controlled trial; VAS: visual analog scale

Table 2. Summary of RCT Results

Study	VAS (at rest)	VAS (in motion)	DASH	Pain-Free Grip Strength
Akcay et al (2020)	12-week follow-up	12-week follow-up	12-week follow-up	12-week follow-up
Dextrose 15% prolotherapy [median (Q1-Q3)]	2.0 (1.0 to 4.0)	3.0 (1.0 to 6.0)	29.1 (5.0 to 55.0)	0.40 (0.30 to 0.42)
Normal saline [median (Q1-Q3)]	3.0 (1.0 to 4.0)	4.0 (3.0 to 6.0)	41.6 (13.0 to 42.5)	0.40 (0.30 to 0.51)
p value (between groups)	NS	NS	NS	NS
Apaydin et al (2020)	12-week follow-up	12-week follow-up	12-week follow-up	12-week follow-up
Dextrose 15% prolotherapy (mean ± SD)	2.7 ± 1.7	3.18 ± 2.3	28.4 ± 13.4	7.3 ± 6.4

Hyaluronic acid (mean ± SD)	3.8 ± 2.09	4.81 ± 1.2	43.5 ± 17.6	4.8 ± 3.2
p value (between groups)	.04	.04	.04	.38

DASH: Disabilities of the Arm, Shoulder, and Hand; NS: nonsignificant; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analog scale.

A double-blind RCT reported by Bayat et al (2019) compared dextrose prolotherapy with corticosteroid injection for chronic lateral epicondylitis.(29) Patients (n=28) received a single injection during the treatment period. There was a significant improvement in VAS pain score at 1- and 3- 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 1 month (p=0.74); however, prolotherapy resulted in significantly better scores at 3 months (p=0.03). At 1 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 3 months (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 quick-DASH score.

Another small (17 subjects) randomized double-blind trial of prolotherapy versus corticosteroid injections for chronic lateral epicondylitis was reported in 2011.(30) Each subject received an injection at baseline followed by a second injection at one month. The 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 three (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.

Achilles Tendonitis

Yelland et al (2011) reported a multicenter randomized trial of prolotherapy or exercises for Achilles tendonitis in 43 patients.(32) Inclusion criteria were diagnosis of unilateral or bilateral mid-portion Achilles tendinosis with pain between two and seven cm proximal to the calcaneal attachment in adults older than 18 years with activity-related pain for at least six 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. 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. This trial was 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).

Rotator Cuff Tendinopathy

Lin et al (2023) conducted a double-blind RCT of 54 patients with chronic subacromial bursitis.(33) Patients were randomized to hypertonic dextrose prolotherapy or subacromial corticosteroid injection. The steroid group had significantly lower VAS scores at weeks 2 (2.9 vs. 4.9; p<.001) and 6 (3.0 vs. 4.3; p<.001) and significantly lower function scores at weeks 2, 6, and 12. Pain scores at 1 weeks were similar between groups (-2 vs. -2.7; p=.387). These results are limited by the small sample size and short duration of follow-up.

Kazempour Mofrad et al (2021) compared periarticular (neurofascial) dextrose prolotherapy and physiotherapy for the short-term treatment of chronic rotator cuff tendinopathy in 66 patients with associated symptoms lasting >3 months.(34) Patients were randomly assigned to physiotherapy, involving 20 minutes of superficial heat using a hot pack followed by transcutaneous electrical nerve stimulation as well as pulsed ultrasound and exercise (n=33), or prolotherapy with hypertonic dextrose 12.5% and 40 mg of 2% lidocaine (n=33). This mixture was injected twice over a 1-week interval around the shoulder joint and to tender joints along the suprascapular nerve. Study outcomes included change in shoulder pain and in a disability index. Overall, 23 patients (70%) in the physiotherapy group and 29 (91%) patients in the prolotherapy group experienced a decrease in pain of 2.8 or greater on a VAS at study end. The difference between the groups was not significant (p=.072). Dextrose prolotherapy was more effective than physiotherapy at alleviating pain at 2 weeks (p<.001) after the intervention; however, both treatments were found to alleviate pain similarly at 3 months (p=.055). Regarding improvement in disability, dextrose prolotherapy was more effective than physiotherapy at 2 weeks and 3 months post-intervention (both p<.001); however, the changes in the physiotherapy group were more sustained. The authors concluded that both treatments were beneficial for chronic rotator cuff tendinopathy, at least in the short term; long-term research is needed to effectively track the pattern of clinical benefits for prolotherapy.

Bertrand et al (2016) reported on an RCT of prolotherapy in rotator cuff tendinopathy with supraspinatus pathology.(35) 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 9 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 enthesis 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 enthesis 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). An important limitation of this study is the single-center design, which may limit generalizability to all patients. Additionally, the enthesis 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.

SUMMARY OF EVIDENCE

For individuals who have musculoskeletal pain (e.g., chronic neck, back pain), osteoarthritic pain, or tendinopathies of the upper or lower limbs who receive prolotherapy, the evidence includes small, randomized trials with inconsistent results. The 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 that the technology results in an improvement in the health outcome.

Supplemental Information

PRACTICE GUIDELINES AND POSITION STATEMENTS

American College of Foot and Ankle Surgeons

A 2017 guideline from the American College of Foot and Ankle Surgeons on acquired infracalcaneal heel pain states that evidence regarding the efficacy and safety of prolotherapy for treatment of plantar fasciitis is uncertain, which makes its use neither appropriate nor inappropriate.(36) The same statement is made for platelet-rich plasma, amniotic tissue, botulinum toxin, and needling.

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.(30) The guideline does not make any recommendation regarding hand osteoarthritis, given lack of trials.

North American Spine Society

A 2020 guideline on low back pain from the North American Spine Society does not provide a recommendation on prolotherapy but states that sacroiliac ligament prolotherapy deserves further study.(38)

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some clinical trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			

NCT03411811	Dextrose Prolotherapy in Chronic Ulnar Wrist Pain Resistant to Usual Care: Comparison to a Naive-to-Treatment Cohort Who Receive Usual Care	60	Jan 2023 (unknown status)
NCT05160532	Intraarticular Dextrose Prolotherapy for Symptomatic Knee Osteoarthritis	160	Mar 2024
NCT05548738	The Efficacy of Ultrasound and Fluoroscopy Guided Caudal Epidural Prolotherapy Versus Steroids for Chronic Pain Management in Failed Back Surgery Syndrome	80	Jun 2024
NCT05984121	Which is Outstanding, Local Ozone Injection or Dextrose Prolotherapy Injection in Chronic Plantar Fasciitis?: A Randomised Controlled Study"	60	Apr 2024 (recruiting)
NCT05821985	Evaluation of the Effect of Dextrose Prolotherapy Versus Dry Needling Therapy for the Treatment of Temporomandibular Joint Anterior Disc Displacement With Reduction (A Randomized Controlled Trial)	40	Nov 2023 (recruiting)
NCT05966948	Hypertonic Dextrose Prolotherapy Versus Normal Saline Intra-articular Injection Among Knee Osteoarthritis With Obese Patient	40	Oct 2023 (completed)
NCT05918146	Effects of Hypertonic Dextrose Prolotherapy on Conventional Physical Therapy in Patients With Subdeltoid Bursitis: a Double-blind, Randomized, Placebo-controlled Study	46	Jun 2024
Unpublished			
NCT01934868	A Comparison of the Long Term Outcomes of Prolotherapy Versus Interlaminar Epidural Steroid Injections (ESI) for Lumbar Pain Radiating to the Leg	110	Apr 2023 (completed)

NCT: national clinical trial

Government Regulations

National

Prolotherapy, Joint Sclerotherapy, and Ligamentous Injections with Sclerosing Agents; Manual 150.7; Publication Number 100.3; Version 1; Effective Date: 9/27/99

Indications and Limitations of Coverage

The medical effectiveness of the above therapies has not been verified by scientifically controlled studies. Accordingly, reimbursement for these modalities should be denied on the ground that they are not reasonable and necessary as required by §1862(a)(1) of the Act.

Local

LCD: **Trigger Points, Local Injections (L34588);** Effective date: 10/01/15; Revision date: 8/31/23;

For all conditions, the actual area must be reported specifically and must be documented in the medical record. Using a non-specific diagnosis code to support injections of multiple areas of the body, rather than more specific diagnosis codes, may result in denial of payment.

- Prolotherapy is not covered by Medicare and cannot be billed under the trigger point injection code.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Orthopedic Applications of Platelet-Rich Plasma
- Recombinant and Autologous Platelet-Derived Growth Factors as a Treatment of Wound Healing and Other Non-Orthopedic Conditions

---

References

1. Dagenais S, Yelland M, Del Mar C et al. Prolotherapy injections for chronic low-back pain. Cochrane Database Syst Rev. 2007; (2):CD004059.
2. Dagenais S, Mayer J, Haldeman S et al. Evidence-informed management of chronic low back pain with prolotherapy. Spine J 2008; 8(1):203-12.
3. Chou R, Atlas SJ, Stanos SP et al. Nonsurgical interventional therapies for low back pain: a review of the evidence for an American Pain Society clinical practice guideline. Spine 2009; 34(10):1078-93.
4. Yelland MJ, Glasziou PP, Bogduk N et al. Prolotherapy injections, saline injections, and exercises for chronic low-back pain: a randomized trial. Spine 2004; 29(1):9-16.
5. Klein RG, Eek BC, DeLong WB et al. A randomized double-blind trial of dextrose-glycerine-phenol injections for chronic, low back pain. J Spinal Disord 1993; 6(1):23-33.
6. Ongley MJ, Klein RG, Dorman TA et al. A new approach to the treatment of chronic low back pain. Lancet 1987; 2(8551):143-6.
7. Bahgat MM, Abdel-Hamid AM. Is dextrose prolotherapy beneficial in the management of temporomandibular joint internal derangement? A systematic review. Cranio. Apr 25 2023: 1-9. PMID 37097125.
8. Kim WM, Lee HG, Jeong CW et al. A randomized controlled trial of intra-articular prolotherapy versus steroid injection for sacroiliac joint pain. J Altern Complement Med 2010; 16(12):1285-90.
9. Reeves KD, Hassanein KM. Long-term effects of dextrose prolotherapy for anterior cruciate ligament laxity. Altern Ther Health Med 2003; 9(3): 58-62.
10. Waluyo Y, Artika SR, Insani Nanda Wahyuni AMAK, et al. Efficacy of Prolotherapy for Osteoarthritis: A Systematic Review. J Rehabil Med. Feb 27 2023; 55: jrm00372. PMID 36847731.
11. Cortez VS, Moraes WA, Taba JV, et al. Comparing dextrose prolotherapy with other substances in knee osteoarthritis pain relief: A systematic review. Clinics (Sao Paulo). 2022; 77: 100037. PMID 35594623
12. Arias-Vazquez PI, Tovilla-Zarate CA, Castillo-Avila RG, et al. Hypertonic Dextrose Prolotherapy, an Alternative to Intra-Articular Injections With Hyaluronic Acid in the Treatment of Knee Osteoarthritis: Systematic Review and Meta-analysis. Am J Phys Med Rehabil. Sep 01 2022; 101(9): 816-825. PMID 34740224
13. Wee TC, Neo EJR, Tan YL. Dextrose prolotherapy in knee osteoarthritis: A systematic review and meta-analysis. J Clin Orthop Trauma. Aug 2021; 19: 108-117. PMID 34046305
14. Sert AT, Sen EI, Esmaeilzadeh S, et al. The Effects of Dextrose Prolotherapy in Symptomatic Knee Osteoarthritis: A Randomized Controlled Study. J Altern Complement Med. May 2020; 26(5): 409-417. PMID 32223554Rabago D, Patterson JJ, Mundt M et al. Dextrose prolotherapy for knee osteoarthritis: a randomized controlled trial. Ann Fam Med 2013; 11(3):229-37.
15. Rabago D, Patterson JJ, Mundt M, et al. Dextrose prolotherapy for knee osteoarthritis: a randomized controlled trial. Ann Fam Med. May-Jun 2013; 11(3): 229-37. PMID 23690322

16. Reeves KD, Hassanein K. Randomized prospective double-blind placebo-controlled study of dextrose prolotherapy for knee osteoarthritis with or without ACL laxity. Altern Ther Health Med 2000; 6(2):68-74, 77-80. PMID 10710805
17. Bayat M, Hojjati F, Boland Nazar NS, et al. Comparison of Dextrose Prolotherapy and Triamcinolone Intraarticular Injection on Pain and Function in Patients with Knee Osteoarthritis - A Randomized Clinical Trial. Anesth Pain Med. Apr 2023; 13(2): e134415. PMID 37601963
18. Jahangiri A, Moghaddam FR, Najafi S. Hypertonic dextrose versus corticosteroid local injection for the treatment of osteoarthritis in the first carpometacarpal joint: a double-blind randomized clinical trial. J Orthop Sci. Sep 2014;19(5):737-743. PMID 25158896
19. Rabago D, Mundt M, Zgierska A, et al. Hypertonic dextrose injection (prolotherapy) for knee osteoarthritis: Long term outcomes. Complement Ther Med. Jun 2015;23(3):388-395. PMID 26051574
20. Reeves KD, Hassanein K. Randomized, prospective, placebo-controlled double-blind study of dextrose prolotherapy for osteoarthritic thumb and finger (DIP, PIP, and trapeziometacarpal) joints: evidence of clinical efficacy. J Altern Complement Med 2000; 6(4):311-20. PMID 10976977
21. Fong HPY, Zhu MT, Rabago DP, et al. Effectiveness of Hypertonic Dextrose Injection (Prolotherapy) in Plantar Fasciopathy: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Arch Phys Med Rehabil. Apr 23 2023. PMID 37098357
22. Ahadi T, Cham MB, Mirmoghtadaei M, et al. The effect of dextrose prolotherapy versus placebo/other non-surgical treatments on pain in chronic plantar fasciitis: a systematic review and meta-analysis of clinical trials. J Foot Ankle Res. Feb 10 2023; 16(1): 5. PMID 36759882
23. Goh SL, Jaafar Z, Gan YN, et al. Efficacy of prolotherapy in comparison to other therapies for chronic soft tissue injuries: A systematic review and network meta-analysis. PLoS One. 2021; 16(5): e0252204. PMID 34038486
24. Chung MW, Hsu CY, Chung WK, et al. Effects of dextrose prolotherapy on tendinopathy, fasciopathy, and ligament injuries, fact or myth?: A systematic review and meta-analysis. Medicine (Baltimore). Nov 13 2020; 99(46): e23201.PMID 33181700
25. Zhu M, Rabago D, Chung VC, et al. Effects of Hypertonic Dextrose Injection (Prolotherapy) in Lateral Elbow Tendinosis: A Systematic Review and Meta-analysis. Arch Phys Med Rehabil. Feb 28 2022. PMID 35240122
26. Scarpone M, Rabago DP, Zgierska A et al. The efficacy of prolotherapy for lateral epicondylosis: a pilot study. Clin J Sport Med 2008; 18(3):248-54. PMID 18469566
27. Akcay S, Gurel Kandemir N, Kaya T, et al. Dextrose Prolotherapy Versus Normal Saline Injection for the Treatment of Lateral Epicondylopathy: A Randomized Controlled Trial. J Altern Complement Med. Dec 2020; 26(12): 1159-1168. PMID 32990454
28. Apaydin H, Bazancir Z, Altay Z. Injection Therapy in Patients with Lateral Epicondylalgia: Hyaluronic Acid or Dextrose Prolotherapy? A Single-Blind, Randomized Clinical Trial. J Altern Complement Med. Dec 2020; 26(12):1169-1175. PMID 32931308
29. Bayat M, Raeissadat SA, Mortazavian Babaki M, et al. Is Dextrose Prolotherapy Superior To Corticosteroid Injection In Patients With Chronic Lateral Epicondylitis?: A Randomized Clinical Trial. Orthop Res Rev. 2019; 11:167-175. PMID 31819675
30. Carayannopoulos A, Borg-Stein J, Sokolof J et al. Prolotherapy versus corticosteroid injections for the treatment of lateral epicondylosis: a randomized controlled trial. PM R 2011; 3(8):706-15. PMID 21871414
31. Rabago D, Best TM, Zgierska AE, et al. A systematic review of four injection therapies for lateral epicondylosis: prolotherapy, polidocanol, whole blood and platelet-rich plasma. Br J Sports Med. Jul 2009; 43(7): 471-81. PMID 19028733

32. Yelland MJ, Sweeting KR, Lyftogt JA et al. Prolotherapy injections and eccentric loading exercises for painful Achilles tendinosis: a randomised trial. Br J Sports Med; Apr 2011; 45(5):421-428. PMID 19549615
33. Lin LC, Lee YH, Chen YW, et al. Comparison Clinical Effects of Hypertonic Dextrose and Steroid Injections on Chronic Subacromial Bursitis: A Double-Blind Randomized Controlled Trial. Am J Phys Med Rehabil. Oct 01 2023; 102(10): 867-872. PMID 36897810
34. Kazempour Mofrad M, Rezasoltani Z, Dadarkhah A, et al. Periarticular Neurofascial Dextrose Prolotherapy Versus Physiotherapy for the Treatment of Chronic Rotator Cuff Tendinopathy: Randomized Clinical Trial. J Clin Rheumatol. Jun 01 2021; 27(4): 136-142. PMID 32975923
35. Bertrand H, Reeves KD, Bennett CJ, et al. Dextrose Prolotherapy Versus Control Injections in Painful Rotator Cuff Tendinopathy. Arch Phys Med Rehabil. Jan 2016; 97(1): 17-25. PMID 26301385
36. Schneider HP, Baca JM, Carpenter BB, et al. American College of Foot and Ankle Surgeons Clinical Consensus Statement: Diagnosis and Treatment of Adult Acquired Infracalcaneal Heel Pain. J Foot Ankle Surg. 2018; 57(2): 370-381. PMID 29284574
37. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Rheumatol. Feb 2020; 72(2):220-233. PMID 31908163
38. North American Spine Society. Diagnosis and Treatment of Low Back Pain. 2020. https://www.spine.org/Portals/0/assets/downloads/ResearchClinicalCare/Guidelines/LowBackPain.pdf. Accessed April 3, 2024.
39. Centers for Medicare and Medicaid Services. National Coverage Determination (NCD) for PROLOTHERAPY, Joint Sclerotherapy, and Ligamentous Injections with Sclerosing Agents (150.7). 1999; https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=15&ncdver=1&SearchType=Advanced&CoverageSelection=Both&NCSelection=NCA%7cCAL%7cNCD%7cMEDCAC%7cTA%7cMCD&PolicyType=Both&s=27&KeyWord=prolotherapy&KeyWordLookUp=Doc&KeyWordSearchType=Exact&kq=true&bc=IAAAACAAAAAAAA%3d%3d&. Accessed April 3, 2024.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through April 3, 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
6/16/03	6/16/03	6/10/03	Joint medical policy established
7/15/05	7/15/05	6/10/05	Routine maintenance
11/1/06	8/28/06	10/30/06	Routine maintenance
1/1/08	10/16/07	11/11/07	Routine maintenance
5/1/09	2/10/09	2/10/09	Routine maintenance
7/1/12	4/10/12	5/18/12	Routine maintenance. Added additional references and rationale.
1/1/14	10/17/13	10/25/13	Routine maintenance
5/1/15	2/17/15	2/27/15	Routine maintenance
7/1/16	4/19/16	4/19/16	Routine maintenance
7/1/17	4/18/17	4/18/17	Routine maintenance
7/1/18	4/17/18	4/17/18	Routine maintenance
7/1/19	4/16/19	4/16/19	Routine maintenance
9/1/19	6/18/19		Routine maintenance
9/1/20	6/16/20		Routine maintenance
9/1/21	6/15/21		Routine maintenance
9/1/22	6/21/22		Routine maintenance
9/1/23	6/13/23		Routine maintenance (slp) Vendor managed: N/A
9/1/24	6/11/24		Routine maintenance (slp) Vendor managed: N/A

Next Review Date: 2nd Qtr, 2025

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN: N/A	Revised: N/A
BCBSM: 12/15/00	Revised: 5/21/01

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: PROLOTHERAPY

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered.
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.