# Prolotherapy

Clinical Policy ID: CCP.1217

Recent review date: 2/2024

Next review date: 6/2025

Policy contains: Musculoskeletal pain; prolotherapy; regenerative injection therapy.

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## Coverage policy

Prolotherapy for musculoskeletal conditions is investigational/not clinically proven, and therefore, not medically necessary.

Limitations

No limitations were identified during the writing of this policy.

Alternative covered services

Surgical treatment.

Non-surgical approaches, including anti-inflammatory medications; physical or occupational therapy; immobilization; using heat or cold; reducing workload and increasing rest, relaxation, and biofeedback techniques; strengthening and conditioning exercises; stretching exercises; and therapeutic massage.

## Background

Musculoskeletal conditions are among the most disabling and costly conditions suffered by Americans of all ages (U.S. Bone and Joint Initiative, 2014). Causes of musculoskeletal pain include the wear and tear of daily activities or trauma to an area, postural strain, repetitive movements, overuse, and prolonged immobilization. Changes in posture or poor body mechanics may bring about spinal alignment problems and muscle shortening, causing other muscles to be misused and become painful. Trauma, back pain, and arthritis are the most common

musculoskeletal conditions in the United States (Orthopaedic Research Society, 2022).

Musculoskeletal pain is best treated by addressing its cause. Non-surgical approaches include anti-inflammatory medications; physical or occupational therapy; immobilization; using heat or cold; reducing workload and increasing rest, relaxation, and biofeedback techniques; strengthening and conditioning exercises; stretching exercises; and therapeutic massage. Integrative therapies such as chiropractic care, acupuncture, or acupressure may be used (National Academies of Sciences, Engineering, and Medicine, 2020).

When conservative treatments fail to alleviate the pain, injection therapies in or around the painful sites may be used. Prolotherapy, also known as regenerative injection therapy, involves injecting an irritant into an injured joint, ligament, or tendon to relieve pain (American Osteopathic Association of Prolotherapy Regenerative Medicine, 2017). Used since the 1930s, prolotherapy (termed from proliferant therapy) has emerged as a treatment option for chronic musculoskeletal injuries. Its mechanism of action has not been clearly established but is hypothesized to stimulate growth factors in the inflammatory healing cascade and promote growth of new ligament or tendon fibers by producing new collagen tissue.

Injection agents may include ingredients such as dextrose, morrhuate sodium, saline, sarapin, procaine, or lidocaine. In recent years, platelet-rich plasma and autologous adult stem cell sources typically taken from bone marrow or adipose (fat) tissue have emerged (American Osteopathic Association of Prolotherapy Regenerative Medicine, 2017). Prolotherapy techniques and injected solutions vary by condition, clinical severity, and practitioner preferences and commonly consist of several injection sessions delivered every three to six weeks over several months (Rabago, 2010).

The U.S. Food and Drug Administration has approved the most commonly used agents, such as dextrose and lidocaine, for injection, but these substances are not specifically approved for prolotherapy for joint and ligamentous injections, making such use off-label. Morrhuate sodium is not currently listed as an approved sclerosing agent (U.S. Food and Drug Administration, 2022).

## Findings

Few professional guidelines address prolotherapy. A guideline on low back pain from the Institute for Health Economics determined that prolotherapy was not recommended as a sole treatment, but could be used as an adjunctive therapy. The most commonly reported adverse events were temporary increases in back pain and stiffness following injections, and some patients had severe headaches suggestive of lumbar puncture, but no serious or permanent adverse events were reported (Institute for Health Economics, 2017). The North American Spine Society (2020) did not issue a recommendation for or against prolotherapy for treatment of low back pain.

The American College of Occupational and Environmental Medicine did not recommend for or against prolotherapy for treatment of lateral epicondylitis (Hegmann, 2013). The American College of Rheumatology/Arthritis Foundation issued a condition recommendation against using prolotherapy in patients with knee or hip osteoarthritis, but issued no recommendation for or against for patients with hand osteoarthritis (Kolasinski, 2020)

Initial systematic reviews found no consistent evidence that prolotherapy injections reduced various types of pain. A recent assessment of systematic reviews and meta-analyses suggest that prolotherapy may be associated with symptom improvement in mild to moderate symptomatic knee osteoarthritis, pending whether further studies uphold existing findings (Rabago, 2017).

Subsequent reviews could not identify consistent evidence of the efficacy of prolotherapy. One review of 58 trials found prolotherapy injections to be superior to placebo but inferior to corticosteroids for long-term pain relief (Sims, 2014).

A systematic review of eight low-quality studies of subjects receiving at least one prolotherapy injection for lower limb tendinitis and fasciopathy found limited support that prolotherapy is effective in reducing pain and improving function. The review also determined that prolotherapy produced similar results in the short, intermediate, and long term compared to alternative treatments, i.e., eccentric loading exercises for Achilles tendinopathy, platelet-rich plasma for plantar fasciopathy, and usual care or lignocaine injections for Osgood-Schlatter disease (Sanderson, 2015).

Several recent systematic reviews found greater evidence of prolotherapy's effectiveness. One consisting of six trials (n = 326) comparing dextrose prolotherapy versus control injections for osteoarthritis over six months found prolotherapy reduced pain compared to controls (by 64%) and local anesthesia (by 62%); the greatest reductions occurred after first injection, but the gains lessened after each month's injection thereafter (Hung, 2016). Another analysis of two trials (n = 258) found dextrose prolotherapy reduced knee osteoarthritis problems by 19% to 22% (Sit, 2016). A third review concluded that prolotherapy might be effective for lateral epicondyalgia, even though this conclusion needed more confirmation (Dong, 2016).

A large study of 14 randomized controlled trials, one case-controlled study, and 18 case series studies for various pain conditions concluded dextrose prolotherapy produced superior outcomes for tendinopathies, knee and finger joint osteoarthritis, and spinal/pelvic pain due to ligament dysfunction but inconclusive outcomes for acute pain, as first-line therapy, and in myofascial pain (Hauser, 2016).

In 2017, prolotherapy was the subject of a meta-analysis of six studies of chronic painful Achilles tendinopathy. Results showed significantly greater improvements for prolotherapy ($P < .001$), along with just one serious and two minor adverse events (Morath, 2018). A systematic review of 10 studies showed improvements in scores for pain, function, and range of motion, both short- and long-term, along with high patient satisfaction of 82% among adults with knee osteoarthritis (Hassan, 2017).

A meta-analysis of 18 studies addressing treatment of patients with rotator cuff tendinopathy showed prolotherapy compared with placebo over the long term of 24 weeks significantly reduced pain (standardized mean difference of 2.44) and significantly improved shoulder function (0.44), as did results for platelet rich plasma. Prolotherapy failed to equal the short-term effect corticosteroids had on pain and shoulder function (Lin, 2019).

A systematic review/meta-analysis of three randomized controlled trials of persons with temporomandibular joint syndrome found a significant reduction in maximum mouth opening after dextrose prolotherapy ($P = .0008$). Prolotherapy was also found to reduce pain significantly compared with placebo ($P = .0007$) (Nagori, 2018).

A systematic review of 18 studies of prolotherapy efficacy for persons with knee osteoarthritis identified moderate supporting evidence for prolotherapy. All other treatment modes were judged to have only limited evidence, including botulinum toxin type A, sodium bicarbonate and calcium gluconate, and low-molecular weight fraction of 5% human serum albumin. Evidence for local anesthetics was conflicting (Hassan, 2018).

A systematic review of five randomized controlled trials (n = 272) analyzed outcomes from prolotherapy using hyperosmolar dextrose solution injection for rotator cuff tendinopathy, six weeks to 12 months after treatment. Control groups consisted of non-operative rehabilitation including physical therapy and medical management (3 studies), supraspinatus saline enthesis injection (1), and corticosteroid injection (1). Pain significantly improved with multi-site injection protocols compared to physical therapy and medical management (Catapano, 2020).

A systematic review of 10 randomized trials (n = 676) compared participants treated with prolotherapy (hypertonic dextrose) for knee osteoarthritis with other treatments (local anesthetics, hyaluronic acid, ozone, platelet-rich plasma or interventional procedures like radiofrequency). Results were mixed: prolotherapy outcomes were better than, similar to, or worse than various other treatments (Arias-Vázquez, 2019).

A systematic review/meta-analysis of nine studies (n = 577) compared regenerative injection therapy to corticosteroids for epicondylitis. Pain reduction was similar at one and two months after therapy ($P$ = .27 and $P$ = .62); and superior for regenerative injections at three and six months ($P$ = .003 and $P$ < .001). Use in daily life was superior for injections at three, six, and 12 months ($P$ = .03, $P$ = .02, and $P$ = .002) (Barnett, 2019).

A systematic review of ten studies (three randomized) of prolotherapy used in participants with chronic patellar tendinopathy showed a decrease in pain with no serious adverse events, leading authors to conclude that prolotherapy may be an effective treatment option to treat pain and improve function (Morath, 2020).

In 2022, we added two systematic reviews and network meta-analyses to the policy (Goh, 2021; Sit, 2021) that confirm previous findings and warrant no policy changes.

Goh (2021) analyzed the effectiveness of prolotherapy in 87 randomized controlled trials (n = 5,859) involving upper limb (74%), lower limb (23%), and truncal/hip (3%) chronic soft tissue injuries. Study quality was mixed ranging from low to moderate. At all time points, prolotherapy had no statistically significant pain benefits over other therapies. Compared to placebo, the effect size for prolotherapy was marginally better for elbow injuries in the medium term (four to eight months) and for shoulder injuries in the short term (less than four months) and long term (more than eight months).

Sit (2021) examined ten randomized controlled trials (n = 336) comparing hypertonic dextrose prolotherapy to placebo in temporomandibular joint dysfunction. All studies had moderate to high risk of bias. In a meta-analysis of five randomized controlled trials, prolotherapy was significantly superior to placebo injections in reducing temporomandibular joint pain at 12 weeks, but showed no statistically significant differences for changes in disability scores.

In 2023, we added several systematic reviews and meta-analyses to the policy. The new evidence from randomized controlled trials included in these analyses examined the safety and effectiveness of hypertonic dextrose prolotherapy alone, in combination with other irritants, or as a noninvasive adjunct compared to nonsurgical interventions for treatment of: lateral epicondylitis (Arias-Vázquez, 2022a; Zhu, 2022); rotator cuff injuries (Zhi, 2022); osteoarthritis of the knee (Arias-Vázquez, 2022b; Chen, 2022; Wang, 2022); and plantar fasciitis (Chutumstid, 2022; Lai, 2021).

The results suggest hypertonic dextrose prolotherapy may be a safe alternative to non-invasive treatments or corticosteroid injections for these indications, when the expected benefits in pain control or function are not achieved. It should be used alone without other irritants, and it typically requires multiple injections and multi-session regimens to maximize its effectiveness. The quality of the evidence was low with moderate-to-high risk of bias, and at times conflicting. All authors recommended studies of higher quality to confirm these findings. No policy changes are warranted.

In 2024, we added several systematic reviews, meta-analyses and a narrative review to the policy. No policy changes are warranted. For plantar fasciitis, a review encompassing eight studies (n = 449) (Ahadi, 2023) and another (Fong, 2023) involving eight randomized controlled trials (n = 469) both highlighted the short-term efficacy of dextrose prolotherapy and hypertonic dextrose injections in reducing pain and improving function. However, these benefits were not sustained in the long term, and the evidence, often marred by high bias, showed mixed results when comparing dextrose treatments to controls, saline injections, or corticosteroids.

A broader systematic review covering 14 randomized controlled trials (n = 936) assessed the efficacy of dextrose injections for osteoarthritis in various joints. This review found dextrose injections comparable or superior to conventional treatments such as saline injections and exercise, but less effective than advanced therapies like platelet-rich plasma (Waluyo, 2023).

Lastly, a narrative review of over 60 studies on prolotherapy (n = 885) looked at chronic conditions like low back pain and tendinopathies, underscoring prolotherapy's potential to yield favorable outcomes compared to

traditional treatments like saline injections and corticosteroids. Across these studies, while short-term benefits were evident, the need for more rigorous, high-quality research to validate long-term efficacy was a recurring theme (Mafhoumi, 2023).

## References

On November 29, 2023, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were (“prolotherapy” (MeSH), “pain management” (MeSH), “musculoskeletal pain,” “prolotherapy,” and “regenerative injection therapy.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.


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## Policy updates

1/2016: initial review date and clinical policy effective date: 4/2016

1/2017: Policy references updated.

1/2018: Policy references updated.

1/2019: Policy references updated. Policy ID changed to CCP.1217.

2/2020: Policy references updated.

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