

PROLOTHERAPY FOR MUSCULOSKELETAL INDICATIONS

Policy Number: SURGERY 060.17 T2

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[Instructions for Use](#) ⓘ

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Related Policy

- [Bone or Soft Tissue Healing and Fusion Enhancement Products](#)

APPLICABLE LINES OF BUSINESS/PRODUCTS

This policy applies to Oxford Commercial plan membership.

NON-COVERAGE RATIONALE

Prolotherapy is unproven and not medically necessary due to insufficient evidence of efficacy.

APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies may apply.

CPT Code	Description
0232T	Injection(s), platelet rich plasma, any site, including image guidance, harvesting and preparation when performed
0481T	Injection(s), autologous white blood cell concentrate (autologous protein solution), any site, including image guidance, harvesting and preparation, when performed <i>CPT® is a registered trademark of the American Medical Association</i>

HCPCS Code	Description
M0076	Prolotherapy

DESCRIPTION OF SERVICES

Prolotherapy is injection of any substance that promotes growth of normal cells, tissues, or organs . Also known as proliferative therapy, non-surgical ligament and tendon reconstruction and regenerative joint injection, is an orthopedic procedure that stimulates the body’s healing processes to strengthen and repair injured and painful joints and connective tissue. (AOAPRM)

There are three types of prolotherapy. Growth factor injection prolotherapy involves the injection of a complex protein that stimulates growth of a certain cell line. Growth factor stimulation prolotherapy causes the body to produce growth factors via dextrose injections. Inflammatory prolotherapy is the injection of a substance that causes activation of the inflammatory cascade to produce growth factors using dextrose, phenol-containing-solutions, and sodium-morrhuate-containing solutions. (AAOM)

Low Back Pain (LBP)

The evidence from published studies indicates that prolotherapy may provide very limited, short-term benefits for chronic back pain (CLBP). While prolotherapy improved CLBP in the short-term, the benefit was not maintained for more than a few weeks and outcomes were similar for placebo and treatment groups at 5-24 months. Prolotherapy may involve a single injection or a series of injections, often diluted with a local anesthetic.

A systematic review by Chou et al. (2009) included 174 articles of which 97 met criteria to assess the benefits and harms of nonsurgical interventional therapies for low back and radicular pain. Of the 97, only 5 addressed prolotherapy. Three of these studies found no difference between prolotherapy and either saline or local anesthetic control injections for short- or long-term (up to 24 months) pain or disability. One higher quality trial found prolotherapy associated with increased likelihood of short-term improvement in pain or disability versus control injection, but both treatment groups received a number of co-interventions including spinal manipulation, local injections, exercises, and walking. In the fifth trial, effects of prolotherapy could not be determined because the prolotherapy group received strong manipulation and the control injection group only light manipulation. The authors concluded that prolotherapy has not been found to be effective for the treatment of low back and radicular pain.

A systematic review by Dagenais et al. (2008) of articles on prolotherapy published from 1997 to 2007 concluded that that prolotherapy is one of a number of treatments recommended for the treatment of CLBP. Prolotherapy has a long history of use, a reasonable but not proven theoretical basis, a low complication rate, and conflicting evidence of efficacy.

In a 2007 Cochrane Review on prolotherapy injections for CLBP, Dagenais et al. concluded that there is conflicting evidence regarding the efficacy of prolotherapy injections for patients with CLBP. When used alone, prolotherapy is not an effective treatment for this condition. When combined with spinal manipulation, exercise, and other co-interventions, prolotherapy may improve CLBP and disability. Conclusions are confounded by clinical heterogeneity amongst studies and by the presence of co-interventions.

Prolotherapy is considered to be contraindicated in patients with metastatic cancer, nonmusculoskeletal pain, spinal anatomical defects, systemic inflammation, morbid obesity, bleeding disorders, low pain threshold, inability to perform post-treatment exercises, chemical dependency, or whole body pain. , Because high doses of a prolotherapy solution containing dextrose 12.5%, glycerin 12.5%, phenol 1.0%, and lidocaine 0.25% may produce a temporary increase in hepatic enzymes, it may not be prudent to not administer these solutions to patients with pre-existing hepatic conditions. (Dagenais et al., 2008)

A systematic review by Hauser et al. examined dextrose (d-glucose) prolotherapy efficacy in the treatment of chronic musculoskeletal pain, searching databases from 1990 to January 2016. Fourteen randomized controlled trials (RCT)s, 1 case-control study, and 18 case series studies met the inclusion criteria. Pain conditions were clustered into tendinopathies, osteoarthritis (OA), spinal/pelvic, and myofascial pain. The RCTs were high quality and found that dextrose injection was superior to controls in Osgood-Schlatter disease, lateral epicondylitis of the elbow, traumatic rotator cuff injury, knee OA, finger OA, and myofascial pain; in biomechanical but not subjective measures in temporal mandibular joint; and comparable in a short-term RCT but superior in a long-term RCT in LBP. Many observational studies were of high quality and reported consistent positive evidence in multiple studies of tendinopathies, knee OA, sacroiliac pain, and iliac crest pain that received RCT confirmation in separate studies. The reviewers concluded that overall, dextrose prolotherapy has been demonstrated to be efficacious and should be considered in patients who fail to respond to conservative therapies as a treatment for pain and dysfunction associated with chronic musculoskeletal conditions, particularly tendinopathies and OA. With inclusion limited to patients with pain >3-6 months in the reviewed studies, the efficacy of prolotherapy for acute (<3 months) musculoskeletal pain cannot be determined. (2016)

Osteoarthritis (OA)***Knee***

van Drumpt et al. (2016) conducted an open label, prospective trial (NCT01773226) assessing safety and efficacy of an injection therapy for individuals with early to moderate OA. Using an Autologous Protein Solution (APS) called nSTRIDE[®], 11 participants who had failed at least one other type of conservative therapy received the injection. Assessment for adverse events (AE) and clinical response outcomes occurred at 1 week, 2 weeks, 1 month, 3 months, and 6 months postinjection. Long-term follow up lasted an average of 18 months. Only mild AEs were reported. Postinjection pain scores were reduced by 83% and 90% at 3 and 6 months, respectively. At 18 months, mean Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index function scores reflected 61% improvement. The authors concluded that a single injection of APS for treatment of early to moderate knee OA had very positive outcomes and that well-controlled, randomized multicenter clinical studies to confirm efficacy are warranted. Study

limitations include the lack of a control group and small sample size, although the study design was deemed adequate to determine feasibility.

Kon et al. (2017) conducted a multicenter, double-blind, RCT to investigate if 1 intra-articular injection of APS can reduce pain and improve function in patients affected by knee OA (NCT02138890). Forty-six patients with unilateral knee OA were randomized into the APS group, which received a single ultrasound-guided injection of APS, and the saline (control) group, which received a single saline injection. Patient-reported outcomes and AEs were collected at 2 weeks and at 1, 3, 6, and 12 months through a variety of assessment tools including the visual analog scale (VAS), WOMAC Index, and Knee injury and Osteoarthritis Outcome Score (KOOS). There were no significant differences in frequency and severity of AEs between groups. The improvement from baseline to 2 weeks and to 1, 3, and 6 months was similar between treatments as well. At 12 months, improvement in WOMAC pain score was 65% in the APS group and 41% in the saline group. There were no significant differences in VAS pain improvement between groups. Significant differences between groups were detected in changes from baseline to 12 months in bone marrow lesion size as assessed on magnetic resonance imaging (MRI) and osteophytes in the central zone of the lateral femoral condyle, both in favor of the APS group. There were no significant differences between the APS and control group in other measured secondary endpoints. The authors concluded that this study supports that a single injection of APS is safe and demonstrates clinical improvement at 1-year in patients affected by knee OA. Treatment with APS or a saline injection provided significant pain relief over the course of the study with differences becoming apparent at between 6 and 12 months after treatment. Study limitations include the need for longer follow up as well as small sample size.

O'Shaughnessey et al. (2014) conducted a multi-center controlled feasibility study (NCT01050894) to determine if blood from OA patients (n=105) could be mechanically processed to form an APS with preferentially increased concentrations of anti-inflammatory versus inflammatory cytokines. Through examination of whole blood taken from control donors and OA donors, it was identified that the APS device system does preferentially increase anti-inflammatory cytokines over inflammatory cytokines. The study also identified that results were no different when using blood from the control or from the OA donors. The authors concluded that these results, combined with findings in previous studies, provides strong support for further investigation of APS as a promising therapy for OA.

A partially blinded controlled trial was performed by Rabago et al. (2013) to assess the relationship between knee OA relative to quality of life (QOL) and intra articular cartilage volume in participants treated with prolotherapy over a 52 week period. It was noted Prolotherapy is an injection therapy reported to improve knee OA-related QOL to a greater extent than blinded saline injections and at-home exercise, but its mechanism of action is unclear. It was noted that the prolotherapy showed improvement in the QOL in those with knee OA compared with the controlled group over the 52 week period. The study concluded that prolotherapy may have a pain-specific disease modifying effect, but still requires further research and testing.

In follow up to the above trial, Rabago et al. also assessed long-term effects of prolotherapy on knee pain, function and stiffness among adults with knee OA through a post clinical-trial, open-label follow-up study. Participants (n=65) received 3-5 monthly interventions and were assessed using the validated WOMAC Index at baseline, 12, 26, 52 weeks, and 2.5 years. Progressive improvement in WOMAC scores were reported at all time intervals. The authors concluded that prolotherapy resulted in safe, significant, progressive improvement of knee pain, function and stiffness scores among most participants through a mean follow-up of 2.5 years and may be an appropriate therapy for patients with knee OA refractory to other conservative care. (2015)

In their Evidence-Based Practice Center Systematic Review Protocol for the Treatment of OA of the Knee, the Agency for Healthcare Review and Quality (AHRQ) does not address intra-articular injected agents such as prolotherapeutic substances. (Newberry et al. 2017)

A Hayes report of published literature on the use of prolotherapy yielded 12 abstracts from multiple study types. While there was sufficient published evidence to evaluate the use of prolotherapy, the study abstracts presented conflicting findings regarding this technology. Therefore, conclusions about the safety and efficacy of prolotherapy could not be made without more in-depth review. (2016)

There are several active clinical trials involving the APS nStride® (Zimmer Biomet) for OA of the knee. For more information, please go to <http://www.clinicaltrials.gov>.

Fingers

Jahangiri et al. compared the advantages of prolotherapy in the treatment of first carpometacarpal osteoarthritis (OA) with those of corticosteroid local injection in a double-blind randomized clinical trial. Sixty participants (60 hands) with OA of the first carpometacarpal joint were assigned equally to 2 groups. For the corticosteroid group, after 2 monthly saline placebo injections, a single dose of 40 mg methylprednisolone acetate (0.5 ml) mixed with 0.5 ml of 2% lidocaine was injected. For the dextrose (DX) group, 0.5 ml of 20% DX was mixed with 0.5 ml of 2% lidocaine and the injection was repeated monthly for 3 months. Pain intensity, hand function and the strength of lateral pinch grip were

measured at the baseline and at 1, 2, and 6 months post-treatment. The 2 groups were comparable at 2 months, but significantly different at 1 month (better results for corticosteroid), and at 6 months (more favorable outcome for DX). After 6 months of treatment, both DX and corticosteroid injection increased functional level, but DX seemed to be more effective. The authors concluded that for the long term, DX seemed to be more advantageous, while the 2 treatments were comparable in the short term. Further research with a large sample size is needed to compare possible complications of corticosteroid/lidocaine vs DX/lidocaine injections in the management of OA. (2014)

Lateral Epicondylitis (LE)

In a comparative effectiveness review by Hayes, prolotherapy using platelet-rich plasma (PRP) is identified as a minimally invasive treatment option for patients with persistent LE that is unresponsive to other conservative measures. Current evidence suggests that PRP may yield some long-term benefits that are not apparent before 6 months, particularly when compared with corticosteroid injection. Once PRP preparations are standardized and best practices are established, trials can identify which factors are associated with better outcomes, yielding more effective PRP preparations and patient selection criteria. (2017)

Dong et al. (2015) conducted a systematic review and meta-analysis comparing many injection therapies (including prolotherapy) for LE. All of the injection treatments showed a trend towards better effects than placebo, and the study authors concluded prolotherapy's superiority would need to be confirmed by more research.

Sims et al. (2014) conducted a systematic review of RCTs examining 11 non-surgical treatments for LE which included prolotherapy. They concluded that the existing literature does not provide conclusive evidence that there is one preferred method of non-surgical treatment for this condition.

A pilot study (Rabago et al., 2013) was conducted assessing dextrose prolotherapy (PrT) for chronic LE. The study design was a three-arm RCT. Twenty-six adults (32 elbows) with chronic LE for 3 months or longer were randomized to ultrasound-guided PrT with dextrose solution, ultrasound-guided PrT with dextrose-morrhuate sodium solution, or watchful waiting ("wait and see"). The primary outcome was the Patient-Rated Tennis Elbow Evaluation (PRTEE) (100 points) at 4, 8, and 16 weeks (all groups) and at 32 weeks (PrT groups). The secondary outcomes included pain-free grip strength and MRI severity score. The participants receiving PrT with dextrose and PrT with dextrose-morrhuate reported improved PRTEE composite and subscale scores at 4, 8, and/or 16 weeks compared with those in the wait-and-see group. At 16 weeks, compared with baseline, the PrT with dextrose and PrT with dextrose-morrhuate groups reported improved composite PRTEE scores by a mean of 18.7 and 17.5 points, respectively. The grip strength of the participants receiving PrT with dextrose exceeded that of the PrT with dextrose-morrhuate and the wait and see at 8 and 16 weeks. There were no differences in MRI scores. Satisfaction was high; there were no AEs. PrT resulted in safe, significant improvement of elbow pain and function compared with baseline status and follow-up data and the wait-and-see control group. This pilot study suggests the need for a definitive trial to validate these results across a larger population.

There are multiple active clinical trials involving the use of prolotherapy in the treatment of LE. For more information, please go to www.clinicaltrials.gov.

Groin Pain

A case series by Topol and Reeves (2008) evaluated the use of prolotherapy in 75 athletes with chronic groin/abdominal pain. Participants received monthly injections of 12.5% dextrose in 0.5% lidocaine for 2 months. Average number of treatments received was 3 (range 1-6). Outcomes were measured using VAS and Nirschl pain phase scale (NPPS). Seventy two athletes completed the full treatment. Follow-up occurred at an average of 26 months (range 6-73). VAS and NPPS improved 82% and 79% respectively. Sixty-six of 72 athletes returned to full sport, and all but 2 of the 66 athletes returned to full sport pain free. The authors found that 81% of the athletes had improvement in pain with 92% returning to unrestricted sports. The study is limited by small sample size and study design. Additional studies are needed to validate these results across a larger and more diverse population.

Temporomandibular Joint (TMJ) Hypermobility

Cömert et al. (2016) conducted a randomized clinical trial involving 30 adult patients with bilateral TMJ hypermobility referred for treatment. They were divided randomly into 2 treatment groups using either saline (placebo group) or dextrose injections (study group). The solution was injected into 5 different TMJ areas in 3 sessions at monthly intervals. The predictor variable was the treatment technique. The outcome variables were VAS evaluations and maximum inter-incisal opening (MIO). Outcome variables were recorded preoperatively and at 12 months postoperatively. The follow-up sample was comprised of 26 subjects, 12 in the placebo group and 14 in the study group. Masticatory efficiency increased and general pain complaints and joint sounds decreased significantly in both groups. MIO decreased significantly only in the study group. Insignificant changes in the other parameters were found for both groups. The authors concluded that after estimating differences between follow-up and baseline outcomes, the mean change in primary outcome variables showed no statistically significant difference between the 2 groups, suggesting that dextrose prolotherapy is no more effective than placebo for TMJ hypermobility.

Refai, et al. (2011) conducted a prospective, randomized, double-blind clinical study with 12 patients to assess the efficacy of dextrose prolotherapy for the treatment of TMJ hypermobility. While therapeutic results were promising, the authors concluded that continued research into prolotherapy's effectiveness with large sample sizes and long-term follow-up is needed.

Lower Limb Tendonopathy

Because their efficacy and potential AEs are unclear, Morath et al. (2018) conducted a systematic review and meta-analysis of available published literature on sclerotherapy (ST) and prolotherapy (PT) for treating Achilles tendinopathy (AT) in athletes. While the initial search yielded 1104 entries, only 13 were human studies. Four RCTs were ranked as having a low risk of selection bias. Three of those reported a statistically significant drop in the VAS score. Positive results regarding pain relief and patient satisfaction were identified in 12 of the 13 studies. Meta-analysis was clearly in favor of the intervention. Only one serious AE and two minor AEs were reported in the entire body of literature. The researchers concluded that ST and PT are safe and may be effective treatment options for AT, however long-term studies and RCTs are still needed to support their recommendation.

Hayes conducted a comparative effectiveness review of peer reviewed literature studying prolotherapy using PRP in the treatment of both AT and plantar fasciitis (PF). Regarding AT, the evidence for use of PRP is limited and does not clearly endorse this treatment over saline. For treatment of PF, PRP may lead to better functional and pain-related outcomes compared with corticosteroids, but evidence for other comparators is limited. Study protocols varied considerably across studies. In the absence of established best practices or standardization of PRP preparations, it is difficult to determine whether prolotherapy holds potential in treating these conditions. (2018)

A systematic review by Sanderson and Bryant (2015) evaluated the effectiveness and safety of prolotherapy injections for management of lower limb tendinopathy and fasciopathy. While no AEs following prolotherapy injections were reported in any study in this review, the authors found limited evidence that prolotherapy injections are a safe and effective treatment for AT, plantar fasciopathy and Osgood-Schlatter disease. More robust research using large, methodologically-sound RCTs is required.

Professional Societies

American Association of Orthopaedic Medicine (AAOM)

In a position statement on *Prolotherapy for the Treatment of Back Pain*, the AAOM states that prolotherapy is a safe and efficacious therapy for the treatment of selected cases of LBP and other chronic myofascial pain syndromes. This conclusion is based upon basic science data showing the effects of prolotherapy in animal models, clinical studies, a long history of clinical use, and increasingly widespread acceptance within the medical community. While they recognize that additional studies regarding the use of prolotherapy for CLBP are necessary to address methodological issues of previous trials, the organization suggests that the same is true for other low back treatment approaches. They believe that prolotherapy can provide pain relief and return of function for many patients. (Klein et al.)

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Prolotherapy is a procedure and, therefore, not subject to FDA regulation. However, any medical devices, drugs, biologics, or tests used as a part of this procedure may be subject to FDA regulation.

Two sclerosing agents have been approved by the FDA: sodium tetradecyl sulfate (Sotradecol[®]), and ethanolamine (Ethamol[®]) for the treatment of varicose veins and esophageal varices. The agents used in the reviewed studies, such as dextrose and lidocaine, are approved for injection by the FDA but are not specifically approved for prolotherapy for joint and ligamentous injections, making such use off-label.

Another agent, sodium morrhuate (Scleromate[®]), is not currently listed as an approved sclerosing agent per the FDA.

NStride[®] (Zimmer Biomet), an autologous protein solution device, does not have FDA approval and is limited to investigational use.

Additional information, under active ingredient name sodium tetradecyl sulfate and ethanolamine, is available at: <http://www.fda.gov/cder/ob/default.htm>. (Accessed February 12, 2018)

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The foregoing Oxford policy has been adapted from an existing UnitedHealthcare national policy that was researched, developed and approved by UnitedHealthcare Medical Technology Assessment Committee. [2018T0498P]

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
12/01/2018	<ul style="list-style-type: none"><li data-bbox="488 268 1260 298">• Simplified non-coverage rationale (no change to guidelines)<li data-bbox="488 298 1182 327">• Archived previous policy version SURGERY 060.16 T2

INSTRUCTIONS FOR USE

This Clinical Policy provides assistance in interpreting UnitedHealthcare Oxford standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare Oxford reserves the right to modify its Policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice.

The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. UnitedHealthcare Oxford Clinical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.