MEDICAL POLICY

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POLICY TITLE	PROLOTHERAPY
POLICY NUMBER	MP-2.061

Original Issue Date (Created):	**August 23, 2002**
Most Recent Review Date (Revised):	**January 28, 2014**
Effective Date:	**April 1, 2014**

I. POLICY

Prolotherapy is considered **investigational** as a treatment of musculoskeletal pain, as there is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Cross-reference

MP-2.033 Blood-Platelet Derived Growth Factors for Wound Healing for platelet-rich plasma injections.
MP-5.048 Diagnosis and Treatment of Sacroiliac Joint Pain

II. PRODUCT VARIATIONS

[N] = No product variation, policy applies as stated
[Y] = Standard product coverage varies from application of this policy, see below

[N] Capital Cares 4 Kids
[N] PPO
[N] HMO
[N] SeniorBlue HMO
[N] SeniorBlue PPO
[N] Indemnity
[N] SpecialCare
[N] POS
[Y] FEP PPO*

* Refer to FEP Medical Policy Manual MP-2.01.26 Prolotherapy. The FEP Medical Policy manual can be found at: www.fepblue.org

III. 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.

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The goal of prolotherapy is to promote tissue repair or growth by prompting release of growth factors, such as cytokines, or 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, glycerine, and phenol, or dextrose alone, often combined with a local anesthetic. Polidocanol and sodium morrhuate, vascular sclerosants, have also been used to sclerose areas of high intratendinous blood flow associated with tendinopathies. Prolotherapy typically involves multiple injections per session conducted over a series of treatment sessions.

A similar approach involves the injection of autologous platelet-rich plasma (PRP), which contains a high concentration of platelet-derived growth factors. Treatment of musculoskeletal pain conditions (e.g., tendinopathies) with PRP is discussed in MP-2.033 Blood-Platelet Derived Growth Factors for Wound Healing.

IV. RATIONALE

Prolotherapy has been investigated as a treatment of various etiologies of musculoskeletal pain, including arthritis, degenerative disc disease, fibromyalgia, tendinitis, and plantar fasciitis. As with any therapy for pain, a placebo effect is anticipated, and thus randomized placebo-controlled trials are necessary to investigate the extent of the placebo effect and to determine whether any improvement with prolotherapy exceeds that associated with a placebo. When this policy was created, there was extensive literature regarding prolotherapy; however, a literature search revealed only 4 randomized placebo-controlled trials. The literature has been updated periodically with searches of the MEDLINE database. The most recent update was performed through July 1, 2013. Key studies to date are described below.

Chronic Neck and Back Pain

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

concluded that prolotherapy was found to be ineffective when used alone for chronic low back pain.

Three randomized trials were identified that focused on the use of injections of dextrose, glycerin, and phenol as a treatment of low back pain. In 1987, Ongley et al. reported on a trial of 81 patients with low back pain who were randomly assigned to receive spinal manipulation plus prolotherapy compared to a control group that received less forceful spinal manipulation, less local anesthesia, and placebo injections of saline. (7) Although improved responses were reported for the treatment group, it is not possible to isolate the possible contribution of the prolotherapy compared to the impact of the different types of spinal manipulation.

In 1993, Klein and colleagues reported on a trial that randomly assigned 79 patients with low back pain to receive a series of 6 weekly injections using either saline or a proliferant solution of dextrose, glycerine, and phenol. (8) Thirty of the 39 patients assigned to the proliferant group achieved a 50% or greater diminution in pain compared to 21 of the 40 in the placebo group. While the incremental benefit of the treatment group was statistically significant (p=0.04), blinding of the treatment groups was not maintained, since those assigned to the proliferant group experienced a clinically recognizable local inflammatory response.

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

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

Osteoarthritis

Rabago et al. reported a randomized controlled trial of prolotherapy for knee osteoarthritis in 2013. (11) This study was supported by the National Center for Complementary and Alternative Medicine (NCCAM). Ninety patients were randomized to blinded injections (3-5 treatments with dextrose prolotherapy or saline) or at-home exercise. All 3 groups showed improvements on the composite Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), with significantly greater improvement in the prolotherapy group (15.3 points) compared to saline and exercise groups (7.6, and 8.2 points, respectively). At 52 weeks, 50% of prolotherapy patients achieved the minimum clinically important difference

(MCID) of a 12-point change in WOMAC, compared to 30% of saline-treated patients and 24% of exercise participants. Knee pain scores also improved more in the prolotherapy group.

In 2000, Reeves and Hassanein reported on 2 trials that used dextrose for the treatment of osteoarthritis. (12) The first trial randomly assigned 68 patients with 111 osteoarthritic knees to receive either 3 bimonthly injections of dextrose or placebo. The patients were evaluated with a visual analog scale (VAS) for pain and swelling, frequency of leg buckling, goniometrically measured flexion, and radiographic measures of joint narrowing. As the data are presented, it is clear that there was significant improvement in both the placebo and treatment groups, but it is difficult to determine the comparative magnitude of improvement between the 2 groups. For example, for the various outcome measures of pain, it appears that there are probably no clinically significant incremental effects of prolotherapy compared to the placebo group. However, for other non-pain outcomes, i.e., swelling; buckling; and flexion range, prolotherapy may be associated with a significant incremental improvement. The various outcome measures were combined and assessed using a Hotelling multivariate analysis. With this statistical measurement, prolotherapy demonstrated a statistically superior overall effect (p=0.015) compared to the control group. It should be recognized that the statistical significance of this measure is most likely due to the improvements in the non-pain symptoms (i.e., swelling, buckling, and flexion range). In summary, it is not known whether the incremental improvement in the non-pain-related outcomes of the prolotherapy group compared to the control group is clinically significant.

In a similarly designed study, the same investigators studied the effectiveness of prolotherapy as a treatment of osteoarthritic thumb and finger joints. (13) A total of 27 patients with 150 osteoarthritic joints were randomly assigned to receive 3 bimonthly injections of either dextrose or water. Patients were evaluated with both VAS for pain and goniometric assessment of joint movement. Since patients had a variable number of joints injected (ranging from 1 to 22), the VAS score for every symptomatic joint in each patient was added together for a total and divided by the number of symptomatic joints to provide an average joint pain score for each patient. There were improvements in pain scores in both the placebo and treatment groups, but the incremental improvement of the treatment group compared to the placebo group did not reach statistical significance. In terms of flexion, the treatment group reported a statistically significant improvement (p=0.043), while the placebo group reported a greater, statistically significant decrease (p=0.011). Therefore, the statistically significant difference in flexion between the 2 groups (p=0.003) was primarily related to the decrease in the control group, with a smaller contribution related to the positive response in the treatment group. In summary, the clinical significance of an isolated finding of improved flexion without a corresponding significant improvement in pain is uncertain.

Tendinopathies of the Upper and Lower Limbs

Lateral Epicondylitis. A 2009 systematic review evaluated injection therapies for lateral epicondylitis (tennis elbow); 2 randomized controlled trials (RCTs) and 1 prospective case

series on prolotherapy were included. (14) One of the randomized trials was referenced as a report from a 2006 conference on complementary and alternative medicine; no authors are listed in the reference, and the study does not appear to be available in the peer-reviewed published literature. The second randomized double-blind placebo-controlled trial involved 20 patients who had elbow pain for at least 6 months and failure of conservative therapy (rest, physical therapy, nonsteroidal anti-inflammatory drugs, and 2 corticosteroid injections) to 3 treatments (over 8 weeks) of prolotherapy or saline injection. (15) There was a significant improvement in pain with prolotherapy injection (from 5.1 to 0.5 on a Likert scale) in comparison with saline injection (4.5 to 3.5). Isometric strength also improved (13 to 31 lb vs. 10 to 11 lb, respectively), but there was no difference in grip strength between the 2 conditions. The authors indicated that this is the first randomized trial of prolotherapy for tendinopathy and that additional research with a larger study population is needed.

A small (17 subjects) randomized double-blind trial of prolotherapy versus corticosteroid injections for chronic lateral epicondylitis was reported in 2011. (16) Each subject received an injection at baseline followed by a second injection at 1 month. VAS for pain, quadruple VAS (QVAS), and Disabilities of the Arm, Shoulder, and Hand questionnaire (DASH) were measured at baseline and at 1, 3, and 6 months. A change of 2 for VAS and 12 for DASH was considered clinically significant. Per protocol analysis showed a significant improvement in VAS and DASH at both 3 (2.38 and 19.89) and 6 months (2.63 and 21.76, both respectively) for the prolotherapy group, while the corticosteroid group showed significant improvement on the DASH at 3 (13.33) and 6 months (15.56). The study was underpowered to detect a significant difference between the prolotherapy and corticosteroid groups for change in VAS, QVAS, or DASH. Larger controlled trials are needed.

Achilles Tendonitis. Yelland et al., an author of Cochrane reviews on this topic, reported a multicenter randomized trial of prolotherapy or exercises for Achilles tendonitis in 43 patients. (17) Inclusion criteria were diagnosis of unilateral or bilateral mid-portion Achilles tendinosis with pain between 2 and 7 cm proximal to the calcaneal attachment in adults older than 18 years with activity-related pain for at least 6 weeks. The sample size was limited by the available resources and slow recruitment rate, resulting in 15 participants in the eccentric loading exercise group, 14 in the prolotherapy group, and 14 in the combined treatment group. Randomization was conducted by a central site and resulted in a lower median duration of pain in the combined treatment group (6 months) than in the exercise alone (21 months) or prolotherapy alone (24 months) groups. An average of 4.4 injections per treatment was directed at tender points in the subcutaneous tissues adjacent to the affected tendon, with 4 to 12 weekly treatments until participants attained pain-free activity or requested to cease treatment. The participants were instructed to perform eccentric loading exercises twice daily in 3 sets of 15 repetitions with the knee straight and 3 sets of 15 repetitions with the knee bent for a period of 12 weeks, with the load progressively increased by adding weights to a backpack. Clinical reviews were performed at 3, 6, and 12 weeks to check technique and progress. Mean increases in the validated Victorian Institute of Sport Assessment – Achilles (VISA-A) score were 23.7 for exercise alone, 27.5 for

prolotherapy alone, and 41.1 for the combined treatment. At 6 weeks and 12 months, these increases were significantly greater for combined treatment (exercise and prolotherapy) than for exercise alone. The predefined minimum clinically important increase of 20 points or more on the VISA-A was obtained by 12 subjects in the combined treatment group and 11 each in the exercise alone and prolotherapy alone groups. This was not significantly different. The percentage of patients achieving full recovery (VISA-A score of 90 or above at 12 months) was 53% for exercise alone, 71% for prolotherapy alone, and 64% for the combined treatment group, but these differences were not significant. Although the authors concluded that prolotherapy may be a cost-effective method to speed recovery in patients with Achilles tendonitis, this study is limited by the combination of a small number of subjects per group, unequal duration of pain in the treatment groups at baseline, and minimal differences in the number of patients showing recovery (11 vs. 12, of 14 or 15, respectively). Additional randomized trials are needed to replicate and extend these findings.

Other Musculoskeletal Pain

Reeves and Hassanein reported on a study of dextrose prolotherapy for anterior cruciate ligament (ACL) laxity. (18) Of 16 evaluable patients, statistically significant improvements were found at 6, 12, and 36 months in ACL laxity, pain, swelling, and knee range of motion. However, this was a small, nonrandomized trial and, as noted above, without placebo control, the extent that improvements with prolotherapy exceed those associated with a placebo cannot be determined.

A 2010 publication by Kim et al. compared intra-articular prolotherapy with intra-articular corticosteroid injection for sacroiliac pain. (19) The randomized double-blind study included 48 patients with sacroiliac joint pain lasting equal to or greater than 3 months, confirmed by equal to or greater than 50% improvement in response to local anesthetic block. The injections were performed on a biweekly schedule (maximum of 3 injections) under fluoroscopic guidance with confirmation of the intra-articular location with an arthrogram. Pain and disability scores were assessed at baseline, 2 weeks, and monthly after completion of treatment. At 2 weeks after treatment, all patients met the primary outcome measure of equal to or greater than 50% reduction in pain scores, and there was no significant difference between the 2 groups. The numerical rating scale for pain was reduced from 6.3 to 1.4 in the prolotherapy group and from 6.7 to 1.9 in the steroid group. The Oswestry Disability Index (ODI) decreased from 33.9 to 11.1 in the prolotherapy group and from 35.7 to 15.5 in the steroid group. Kaplan-Meier survival analysis showed a significantly greater percentage of patients with sustained relief following prolotherapy. At 6 months after treatment, 63.6% of patients in the prolotherapy group reported equal to or greater than 50% improvement from baseline in comparison with 27.2% of the steroid group. At 15 months after treatment, 58.7% of patients in the prolotherapy group reported relief equal to or greater than 50% in comparison with 10.2% of the steroid group. Key differences between this and other studies on prolotherapy were the selection of patients using a diagnostic sacroiliac joint block and the use of an arthrogram to confirm the location

of the injection. Additional trials are needed to confirm the safety and efficacy of this procedure.

Ongoing Clinical Trials

A search of online site ClinicalTrials.gov in July 2013 identified the following randomized trials on prolotherapy:

- The Efficacy of Prolotherapy in Osteoarthritic Knee Pain (NCT00085722) is listed as ongoing but is currently not recruiting participants. This randomized placebo-controlled study is sponsored by the National Center for Complementary and Alternative Medicine (NCCAM) and will determine whether prolotherapy can decrease pain and disability from knee osteoarthritis. The posting lists an estimated enrollment of 111 subjects, with July 2013 as the completion date for primary outcome measures.
- Prolotherapy for the Treatment of Chronic Lateral Epicondylitis (NCT00674622) is a randomized placebo-controlled trial sponsored by NCCAM. The study is listed as completed as of June 14, 2012 with 67 subjects.
- NCT01326351 is described as a Phase IV randomized double-blind sham controlled trial of prolotherapy combined with a physiotherapy program for plantar fasciitis. The study is sponsored by Réseau de Santé Vitalité Health Network in Canada. The posting lists an estimated enrollment of 60 subjects with completion expected in 2012. Recruitment for this study had not begun as of April 2011. The current status is unknown.
- NCT01402011 is a randomized study of prolotherapy for injured ligaments and tendons of the shoulder. The study has an estimated enrollment of 74 subjects with completion expected June 2013. The current status of the study is unknown.
- NCT01617356 is a randomized trial of prolotherapy versus saline injection for the treatment of temporomandibular dysfunction. The study began enrollment of a projected 42 subjects in June 2012 and has an estimated study completion date in 2014.

Summary

The literature on prolotherapy consists of small randomized trials on a variety of pain syndromes, with inconsistent results. The body of scientific evidence does not permit conclusions concerning the effect of prolotherapy on health outcomes for chronic neck or back pain, tendinopathies of the upper or lower limbs, osteoarthritic pain, or other musculoskeletal pain conditions. Therefore, prolotherapy is considered investigational.

Medicare National Coverage

The Coverage Issues Manual (CIM) #35-13 states that prolotherapy, joint sclerotherapy, and ligamentous injections with sclerosing agents are not covered, noting that the medical effectiveness of these therapies has not been verified by scientifically controlled studies. In 1999, on request for reconsideration of coverage of prolotherapy for treatment for chronic

low back pain, Medicare retained its decision for noncoverage of prolotherapy again, citing a lack of scientific evidence on which to base a decision. (20)

V. DEFINITIONS

CYTOKINES refer to one or more than one hundred (100) distinct proteins produced primarily by white blood cells. They provide signals to regulate immunological aspects of cell growth and function during both inflammation and specific immune response.

VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member's individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member's benefit information or contact Capital for benefit information.

VII. DISCLAIMER

Capital's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. REFERENCES

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Other

Taber's Cyclopedic Medical Dictionary, 20h edition.

IX. CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational; therefore not covered:

HCPCS Code	Description
M0076	PROLOTHERAPY

Investigational when used for prolotherapy; therefore not covered:

CPT Codes®								
20550	20551	20552	20999	27096	64493	64494	66495	0232T

X. POLICY HISTORY

MP 2.061	**CAC 10/28/03**
	CAC 7/26/05
	CAC 7/25/06
	CAC 7/31/07
	CAC 7/29/08
	CAC 7/28/09 Consensus Review
	CAC 9/20/10 Adopt BCBSA.

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	CAC 10/25/11 Consensus Review. FEP variation changed to refer to FEP policy manual
	CAC 1/29/13 Consensus review. References updated; no changes to policy statement. CODES REVIEWED 11/27/12 KLR
	CAC 1/28/14 Consensus review. References updated; no changes to policy statement. Rationale added.

[Note: Final page is signature page and is kept on file, but not issued with Policy.]