Clinical Policy Bulletin: Prolotherapy

Number: 0207

Policy

Aetna considers prolotherapy (also known as proliferant therapy, proliferation therapy, joint sclerotherapy, or reconstructive ligament therapy) experimental and investigational for all indications, including the following (not an all-inclusive list), because there is inadequate evidence of its effectiveness:

- Achilles tendinosis
- Back pain Coccynodynia
- Epicondylitis
- Iliotibial band syndrome. Knee ligament instability
- Knee osteoarthritis
- Myofascial pain Neuropathic pain
- Osteomyelitis pubis
- Sacroiliac joint pain
- Temporomandibular joint syndrome
- Tendinopathies

Aetna considers prolozone therapy experimental and investigational for any diagnosis because there is no peer-reviewed published clinical literature regarding its effectiveness.

Aetna considers Sarapin, an herbal extract that has been used as a sclerosant in prolotherapy, experimental and investigational for all indications because there is inadequate evidence of its effectiveness.

Note: Ongley solution (also known as P2G) is a proliferant solution.

Background

Prolotherapy refers to the injection of sclerosing solutions into joints, muscles, or ligaments. The effectiveness of prolotherapy has not been verified by scientifically controlled studies. As early as 1978, the Medical Procedures Appropriateness Program of the Council of Medical Specialty Services (CMSS), based on input from the American Academy of Orthopedic Surgeons, the American Association of Neurological Surgeons, and the American College of Physicians, concluded that prolotherapy had not been shown to be effective. Additionally, the Canadian Coordinating Office for Health Technology Assessment (2004) stated that "evidence from further controlled clinical trials of prolotherapy is clearly needed."
An assessment of prolotherapy prepared for the California Technology Assessment Forum (CTAF) concluded that prolotherapy does not meet CTAF's assessment criteria (Feldman, 2004). The assessment concluded "only one early study (Ongley et al, 1987) was able to demonstrate conclusively that prolotherapy was significantly superior to placebo for treatment of chronic low back pain. Subsequent research has not been able to replicate this finding. It is therefore not possible to conclude from the published literature that prolotherapy is superior to placebo injection for the treatment of chronic low back pain."

In the 1960s, Dr. Milne Ongley employed a more sclerosant than proliferative solution, as was common. Ongley searched the New Zealand Formulary and found an approved solution containing 50 % dextrose, 30 % glycerin, and 2.5 % phenol. It became known as "Ongley solution" or P2G.

http://www.medscape.com/viewarticle/707539. The study by Ongley et al (1987) was one of the few studies in the treatment of LBP to show a dramatic difference between treatment and placebo groups. There were several major drawbacks with the study by Ongley et al: (i) Subjects in the treatment group received an initial treatment of up to 60 ml lidocaine 0.5 % injection into the lumbosacral area compared with only 10 ml for the control group, (ii) The treatment group also received 50-mg triamcinolone injection into the gluteus medius compared with lidocaine 0.5 % injection for the control group, and (iii) the treatment group received actual spinal manipulation versus sham manipulation for the control group. The findings of the Ongley study were confounded by the use of combinational treatments (including spinal manipulation as well as triamcinolone injections); these findings need to be validated.

Ongley et al (1988) examined the effectiveness of prolotherapy for the treatment of ligament instability of knees. The study was conducted during a 9-month period in a private orthopedic office. A total of 30 patients presented with knee pain during the enrollment period, but 5 knees (in 4 patients) were selected because of substantial and reproducible ligament instability. After informed consent had been given specific measurements were obtained. All measurements were taken by 1 researcher. The patients underwent multiple injections and were followed routinely. After 9 months repeated measurements were obtained. Subjective symptoms were recorded at entry and exit from the study. Ligament stability was measured by a commercially available computerized instrument that measures ligament function objectively and reliably in a complete 3-dimensional format. It consists of a chair equipped with a 6-component force platform and an electrogoniometer. With computer-integrated force and motion measurements, a standardized series of clinical laxity tests can be performed and an objective report obtained. Prior studies have compared clinical testing with objective tests and have established reproducibility. The proliferant solution is made up as follows:

Dextrose 25 % (694 mosmol/L), glycerine 25% (2,720 mosmol/L), phenol 2.5 % (266 mosmol/L), and pyrogen-free water to 100 %. At the time of injection it is diluted with an equal volume of 0.5 % lidocaine. The proliferant injections are "peppered" into the lax ligament(s) usually at 2-weekly intervals, each offending ligament being treated an average of 4 times. A total of between 30 and 40 cc of the proliferant solution is injected into the appropriate portion of the joint ligaments. These researchers reported that their protocol was successful in reducing the laxity of unstable knees in this study group. All patients demonstrated improvement in measurable objective data. In addition, the subjective improvement and activity level was markedly improved. They noted that this study was one of the first to measure clinical outcome by the 3-dimensional computerized instrument. They believed this technique will help to evaluate intervention in unstable knees; and prolotherapy provided a well-tolerated new dimension in the treatment of ligamentous instability of the knee. It was well-
tolerated, as the preliminary results demonstrated. Moreover, they stated that the drawbacks of this study were the small number of subjects and the study design. They stated that a randomized control without injection therapy and only physiotherapy will be necessary to confirm these findings. The authors believed, however, that these results were very encouraging and provided the scientific format for further research.

An UpToDate review on “Overview of the management of overuse (chronic) tendinopathy” (Khan and Scott, 2014) lists prolotherapy as one of the investigational therapies; it noted that larger, randomized trials are needed to assess this treatment before it can be recommended.

In a systematic review of prolotherapy for chronic musculoskeletal pain, Rabago et al (2005) concluded that there are limited high-quality data supporting the use of prolotherapy in the treatment of musculoskeletal pain or sport-related soft tissue injuries. Positive results compared with controls have been reported in non-randomized and randomized controlled trials (RCTs). Further investigation with high-quality RCTs with non-injection control arms in studies specific to sport-related and musculoskeletal conditions is necessary to determine the effectiveness of prolotherapy.


In a Cochrane review on prolotherapy injections for chronic LBP, Degenais et al (2007) concluded that there is conflicting evidence regarding the effectiveness of prolotherapy injections for patients with chronic LBP. When used alone, prolotherapy is not an effective treatment for chronic LBP. When combined with spinal manipulation, exercise, and other co-interventions, prolotherapy may improve chronic LBP and disability. These researchers noted that conclusions are confounded by clinical heterogeneity among studies and by the presence of co-interventions.

Also, a practice guideline from the American Pain Society on low LBP (Chou et al, 2009) stated that prolotherapy is not recommended for persistent non-radiculor LBP.

Furthermore, the clinical practice guideline on “Acute Low Back Problems in Adults” by the Agency for Health Care Policy and Research does not recommend ligamentous and sclerosant injections in the treatment of patients with acute low back pain (LBP). In a report, Yelland et al (2004) concluded that prolotherapy is no more effective than saline injections for the treatment of chronic LBP.

An UpToDate review on “Subacute and chronic low back pain: Nonsurgical interventional treatment” (Chou, 2014) states that “One systematic review included five trials of prolotherapy, compared with local anesthetic or saline injections, for chronic low back pain. There was no difference for short- or long-term pain or disability between prolotherapy and control intervention in three of the trials. Results from one trial that demonstrated short-term benefit for prolotherapy are difficult to interpret, because patients also received a number of co-interventions including forceful manipulation, injection of tender points, and exercise. A fifth trial was confounded by differences in the type of manipulation given to patients in the prolotherapy and control groups. Based on these trial results, a guideline from the American Pain Society recommends against prolotherapy for chronic low back pain”.

http://qawww.aetna.com/cpb/medical/data/200_299/0207_draft.html  04/22/2015
In addition, guidelines on low back pain from the American College of Occupational and Environmental Medicine (2007) have concluded that the use of prolotherapy for acute, subacute, chronic or radicular pain syndromes is not recommended.

Dagenais et al (2005) stated that results from clinical studies published to date indicate that prolotherapy may be effective at reducing spinal pain. Great variation was found in the injection and treatment protocols used in these studies that preclude definite conclusions. Future research should focus on those solutions and protocols that are most commonly used in clinical practice and have been used in trials reporting effectiveness to help determine which patients, if any, are most likely to benefit from this treatment (Dagenais et al, 2005).

Khan and colleagues (2008) presented the results of dextrose prolotherapy undertaken for chronic non-responding coccyxodynia in 37 patients (14 men and 23 women, mean age of 36 years). Patients with chronic coccyxodynia not responding to conservative treatment for more than 6 months were included; 27 of them had received local steroid injections. A visual analog score (VAS) was recorded for all patients before and after injection of 8 ml of 25 % dextrose and 2 ml of 2 % lignocaine into the coccyx. In 8 patients with a VAS of more than 4 after the second injection, a third injection was given 4 weeks later. The mean VAS before prolotherapy was 8.5. It was 3.4 after the first injection and 2.5 after the second injection. Minimal or no improvement was noted in 7 patients; the remaining 30 patients had good pain relief. The authors concluded that dextrose prolotherapy is an effective treatment option in patients with chronic, recalcitrant coccyxodynia and should be used before undergoing coccygectomy. They stated that randomized studies are needed to compare prolotherapy with local steroid injections or coccygectomies.

In a pilot study, Scarpone et al (2008) examined the effectiveness of prolotherapy in the treatment of lateral epicondylosis. Subjects received injections of a solution made from 1 part 5 % sodium morrhuate, 1.5 parts 50 % dextrose, 0.5 parts 4 % lidocaine, 0.5 parts 0.5 % sensorcaine and 3.5 parts normal saline. Controls received injections of 0.9 % saline. Three 0.5-mi injections were made at the supracondylar ridge, lateral epicondyle, and annular ligament at baseline and at 4 and 8 weeks. The primary outcome was resting elbow pain (0 to 10 Likert scale). Secondary outcomes were extension and grip strength. Each was performed at baseline and at 8 and 16 weeks. One-year follow-up included pain assessment and effect of pain on activities of daily living. The groups were similar at baseline. Compared to controls, prolotherapy-treated subjects reported improved pain scores (4.5 +/- 1.7, 3.6 +/- 1.2, and 3.5 +/- 1.5 versus 5.1 +/- 0.8, 3.3 +/- 0.9, and 0.5 +/- 0.4 at baseline and at 8 and 16 weeks, respectively). At 16 weeks, these differences were significant compared to baseline scores within and among groups (p < 0.001). Prolotherapy subjects also reported improved extension strength compared to controls (p < 0.01) and improved grip strength compared to baseline (p < 0.05). Clinical improvement in prolotherapy-treated subjects was maintained at 52 weeks. There were no adverse events. The authors concluded that prolotherapy with dextrose and sodium morrhuate was well-tolerated, effectively decreased elbow pain, and improved strength testing in subjects with refractory lateral epicondylosis compared to control group injections. The findings of this pilot study (with a small sample size) need to be validated by more research.

In a systematic review on injection therapies for lateral epicondylosis (LE), Rabago and colleagues (2009) stated that there is strong pilot-level evidence supporting the use of prolotherapy in the treatment of LE. Moreover, they noted that rigorous studies of sufficient sample size, assessing these injection therapies using validated clinical, radiological and biomechanical measures, and tissue
injury/healing-responsive biomarkers, are needed to determine the long-term effectiveness and safety, and whether these techniques can play a definitive role in the management of LE and other tendinopathies.

In a systematic review and meta-analysis, Krogh et al (2013) evaluated the comparative effectiveness and safety of injection therapies in patients with lateral epicondylitis. Randomized controlled trials comparing different injection therapies for lateral epicondylitis were included provided they contained data for change in pain intensity (primary outcome). Trials were assessed using the Cochrane risk of bias tool. Network (random effects) meta-analysis was applied to combine direct and indirect evidence within and across trial data using the final end point reported in the trials, and results for the arm-based network analyses are reported as standardized mean differences (SMDs). A total of 17 trials (1,381 participants; 3 [18 %] at low-risk of bias) assessing injection with 8 different treatments -- glucocorticoid (10 trials), botulinum toxin (4 trials), autologous blood (3 trials), platelet-rich plasma (2 trials), and polidocanol, glycosaminoglycan, prolotherapy, and hyaluronic acid (1 trial each) -- were included. Pooled results (SMD [95 % CI]) showed that beyond 8 weeks, glucocorticoid injection was no more effective than placebo (-0.04 [-0.45 to 0.35]), but only 1 trial (which did not include a placebo arm) was at low-risk of bias. Although botulinum toxin showed marginal benefit (-0.50 [-0.91 to -0.08]), it caused temporary paresis of finger extension, and all trials were at high-risk of bias. Both autologous blood (-1.43 [-2.15 to -0.71]) and platelet-rich plasma (-1.13 [-1.77 to -0.49]) were also statistically superior to placebo, but only 1 trial was at low-risk of bias. Prolotherapy (-2.71 [-4.60 to -0.82]) and hyaluronic acid (-5.58 [-6.35 to -4.82]) were both more efficacious than placebo, whereas polidocanol (0.39 [-0.42 to 1.20]) and glycosaminoglycan (-0.32 [-1.02 to 0.38]) showed no effect compared with placebo. The criteria for low-risk of bias were only met by the prolotherapy and polidocanol trials. The authors concluded that this systematic review and network meta-analysis of RCTs found a paucity of evidence from unbiased trials on which to base treatment recommendations regarding injection therapies for lateral epicondylitis.

In a pilot study, Rabago et al (2013) evaluated the effectiveness of 2 prolotherapy (PrT) solutions for chronic lateral epicondylitis. This study was a 3-arm RCT. A total of 26 adults (32 elbows) with chronic lateral epicondylitis for 3 months or longer were randomized to ultrasound-guided PrT with dextrose solution, ultrasound-guided PrT with dextrose-morphuate sodium solution, or watchful waiting ("wait-and-see"). The primary outcome was the Patient-Rated Tennis Elbow Evaluation (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 magnetic resonance imaging severity score. The participants receiving PrT with dextrose and PrT with dextrose-morphuate reported improved Patient-Rated Tennis Elbow Evaluation composite and subscale scores at 4, 8, and/or 16 weeks compared with those in the wait-and-see group (p < 0.05). At 16 weeks, compared with baseline, the PrT with dextrose and PrT with dextrose-morphuate groups reported improved composite Patient-Rated Tennis Elbow Evaluation scores by a mean (SE) of 18.7 (9.6; 41.1 %) and 17.5 (11.6; 53.5 %) points, respectively. The grip strength of the participants receiving PrT with dextrose exceeded that of the PrT with dextrose-morphuate and the wait-and-see at 8 and 16 weeks (p < 0.05). There were no differences in magnetic resonance imaging scores. Satisfaction was high; there were no adverse events. The authors concluded that 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. They stated that the findings of this pilot study suggested the need for a definitive trial.
An UpToDate review on “Epicondylitis (tennis and golf elbow)” (Jayanthi, 2014) states that “The role of prolotherapy in the treatment of epicondylitis warrants further investigation.”

Sims et al (2014) stated that non-surgical approaches to treatment of lateral epicondylitis are numerous. These investigators examined RCTs of these treatments. Numerous databases were systematically searched from earliest records to February 2013. Search terms included “lateral epicondylitis”, “lateral elbow pain”, “tennis elbow”, “lateral epicondylalgia”, and “elbow tendinopathy” combined with “randomized controlled trial”. Two reviewers examined the literature for eligibility via article abstract and full text. A total of 58 articles met eligibility criteria: (i) a target population of patients with symptoms of lateral epicondylitis; (ii) evaluation of treatment of lateral epicondylitis with the following non-surgical techniques: corticosteroid injection, injection technique, iontophoresis, botulinum toxin A injection, prolotherapy, platelet-rich plasma or autologous blood injection, bracing, physical therapy, shockwave therapy, or laser therapy; and (iii) a randomized controlled trial design. Lateral epicondylitis is a condition that is usually self-limited. There may be a short-term pain relief advantage found with the application of corticosteroids, but no demonstrable long-term pain relief. Injection of botulinum toxin A and prolotherapy are superior to placebo but not to corticosteroids, and botulinum toxin A is likely to produce concomitant extensor weakness. Platelet-rich plasma or autologous blood injections have been found to be both more and less effective than corticosteroid injections. Non-invasive treatment methods such as bracing, physical therapy, and extra-corporeal shockwave therapy do not appear to provide definitive benefit regarding pain relief. Some studies of low-level laser therapy show superiority to placebo whereas others do not. The authors concluded that there are multiple RCTs for non-surgical management of lateral epicondylitis, but the existing literature does not provide conclusive evidence that there is one preferred method of non-surgical treatment for this condition. Moreover, they stated that lateral epicondylitis is a condition that is usually self-limited, resolving over a 12- to 18-month period without treatment.

An evidence review of prolotherapy from the Veterans Administration Technology Assessment Program (VATAP) (Adams, 2008) stated: “Although proponents have advocated the use of prolotherapy for a range of indications, relatively few clinical uses have been studied systematically or published in the peer-reviewed literature. Results of the most recent systematic reviews are inconclusive for demonstrating the effectiveness of prolotherapy for treatment of musculoskeletal pain, and new evidence from case series would not alter these conclusions. The majority of published experimental studies have included conservative therapy with prolotherapy for relief of chronic low back pain, and to a lesser extent, osteoarthritis of the knee with varying results. Sample sizes have been insufficient on which to base national policy decisions.”

The VATAP assessment also noted that the existing evidence base for prolotherapy shows wide variation in patient selection criteria (Adams, 2008). The review noted that, in case series, findings from physical examination by a prolotherapist are part of the inclusion criteria, whereas all entry criteria from randomized controlled clinical trials were diagnosis-driven. The positive results seen in these case series may, in part, reflect careful selection criteria that a prolotherapist would employ in clinical practice using both diagnostic and examination findings.
The VATAP assessment stated that greater attention needs to be paid to using an appropriate control group (Adams, 2008). The report found that RCTs to date have employed control therapies with injection, which may invoke a response irrespective of injectant used, resulting in similar clinical improvement observed across study arms, while other RCTs have used control groups with very different treatment regimens such that it is not possible to attribute improvement in outcomes to prolotherapy alone.

The VATAP found that prolotherapy appears to have a safety profile comparable to that of other needling procedures, when performed by a skilled prolotherapist, but treatment protocols varied considerably across studies (Adams, 2008). The VATAP notes that, up to now, education and training for prolotherapists have relied on continuing education programs and mentoring and have not been standardized.

The VATAP report stated that prolotherapy along with conservative interventions (e.g., physiotherapy) appears to offer some pain relief when administered by a skilled prolotherapist in patients with LBP who are refractory to other treatments, but its independent role in these patients remains to be determined (Adams, 2008). The report stated that, given the increasing interest in this intervention, additional research and monitoring are warranted to clarify the safety profile and to determine the optimal proliferant, dosage and schedule, appropriate patient selection criteria, and the independent role of prolotherapy for a number of indications for which there are limited nonsurgical options for persons seeking chronic pain relief. The report stated that ongoing clinical trials of prolotherapy should help define its clinical use.

Guidelines on chronic pain from the American College of Occupational and Environmental Medicine (2008) have concluded that the use of prolotherapy for neuropathic or myofascial pain is not recommended. American College of Occupational and Environmental Medicine (2011) guidelines on hand, wrist, and forearm disorders were unable to make a recommendation about the use of prolotherapy because of insufficient evidence.

In a prospective RCT, Kim and colleagues (2010) evaluated the efficacy and long-term effectiveness of intra-articular prolotherapy in relieving sacroiliac joint pain, compared with intra-articular steroid injection. The study included patients with sacroiliac joint pain, confirmed by greater than or equal to 50 % improvement in response to local anesthetic block, lasting 3 months or longer, and who failed medical treatment. The treatment involved intra-articular dextrose water prolotherapy or triamcinolone acetonide injection using fluoroscopic guidance, with a bi-weekly schedule and maximum of 3 injections. Pain and disability scores were assessed at baseline, 2 weeks, and monthly after completion of treatment. The numbers of recruited patients were 23 and 25 for the prolotherapy and steroid groups, respectively. The pain and disability scores were significantly improved from baseline in both groups at the 2-week follow-up, with no significant difference between them. The cumulative incidence of greater than or equal to 50 % pain relief at 15 months was 58.7 % (95 % confidence interval [CI]: 37.9 % to 79.5 %) in the prolotherapy group and 10.2 % (95 % CI: 6.7 % to 27.1 %) in the steroid group, as determined by Kaplan-Meier analysis; there was a statistically significant difference between the groups (log-rank p < 0.005). The authors concluded that intra-articular prolotherapy provided significant relief of sacroiliac joint pain, and its effects lasted longer than those of steroid injections. They stated that further studies are needed to confirm the safety of the procedure and to validate an appropriate injection protocol.
Choi et al (2011) examined the most current evidence for treatment options in athletes with osteitis pubis and osteomyelitis pubis, attempting to determine which options provide optimal pain relief with rapid return to sport and prevention of symptom reoccurrence. Three databases -- MEDLINE, Cochrane Database of Systematic Reviews and CINAHL -- were searched using the OVID interface for all years between 1985 and May 2008. References were analysed from included studies, and additional relevant articles were obtained for inclusion. Inclusion criteria included (i) humans only, (ii) subjects had no apparent risk factors for development of osteitis pubis or osteomyelitis of the pubic symphysis other than athletic involvement, (iii) both physical examination findings and diagnostic imaging were used to confirm either diagnosis, and (iv) a definitive treatment strategy was identifiable for management of osteitis pubis or osteomyelitis of the pubic symphysis. In total, 25 articles were included in the review. There were no RCTs identified with this study’s search strategy. A total of 195 athletes were diagnosed as having osteitis pubis (186 males, 9 females) and treated with either conservative measures/physical therapy, local injection with corticosteroids and/or local anesthetic, dextrose prolotherapy, surgery or antibiotic therapy. Six case reports/series described conservative treatment measures (physical therapy, rest, non-steroid anti-inflammatory drugs). Four case series explored the use of corticosteroid injections in treatment. One case series described the use of dextrose prolotherapy as a treatment modality. Six case series described various surgical techniques (pubic symphysis curettage, polypropylene mesh placement and pubic bone stabilisation) in treatment. Ten case reports/series (10 subjects) outlined antibiotic treatment of osteomyelitis of the pubic symphysis. The authors concluded that current medical literature shows only level 4 evidence of the treatment for osteitis pubis in 24 case reports/series in athletes. Without any direct comparison of treatment modalities, it is difficult to determine which individual treatment option is the most efficacious. They stated that further study comparing the different treatment options is needed to determine which modality provides the fastest return to sport.

In a prospective, randomized, double-blind, placebo-controlled clinical study, Rafai et al (2011) evaluated the effectiveness of dextrose prolotherapy for the treatment of temporomandibular joint (TMJ) hypermobility. A total of 12 patients with painful subluxation or dislocation of the TMJ were randomly assigned to 1 of 2 equal-sized groups. Patients in the active group received 4 injections of dextrose solution (2 ml of 10 % dextrose and 1 ml of 2 % mepivacaine) for each TMJ, each 6 weeks apart, whereas patients in the placebo group received injections of placebo solution (2 ml of saline solution and 1 ml of 2 % mepivacaine) on the same schedule. A verbal scale expressing TMJ pain on palpation, maximal mouth opening (MMO), clicking sound, and frequency of luxations (number of locking episodes per month) were assessed at each injection appointment just before the injection procedure and 3 months after the last injection. The collected data were then statistically analyzed. By the end of the study, each group showed significant improvement in TMJ pain on palpation and number of locking episodes and insignificant improvement in clicking sound. With the exception of the MMO, there were no statistically significant differences throughout the study intervals between the active and placebo groups. The active group showed a significant reduction in MMO at the 12th week post-operatively. Differences compared with mean baseline value remained significant at the end of the follow-up period. On the other hand, the placebo group showed an insignificant difference in MMO throughout the study periods. For the last 2 intervals, the placebo group showed statistically significantly higher mean MMO values than the active group. By the end of the 12th post-operative week, the percentages of decrease in MMO were significantly
greater in the active group. The authors concluded that prolotherapy with 10 % dextrose appears promising for the treatment of symptomatic TMJ hypermobility, as evidenced by the therapeutic benefits, simplicity, safety, patients’ acceptance of the injection technique, and lack of significant side effects. However, these investigators stated that continued research into prolotherapy’s effectiveness in patient populations with large sample sizes and long-term follow-up is needed.

In a prospective, uncontrolled study with 1-year follow-up, Rabago et al (2012) examined if prolotherapy would improve pain, stiffness, and function in adults with symptomatic knee osteoarthritis (KOA) compared to baseline status. Adults with at least 3 months of symptomatic KOA, recruited from clinical and community settings, participated in the study. Participants received extra-articular injections of 15 % dextrose and intra-articular prolotherapy injections of 25 % dextrose at 1, 5, and 9 weeks, with as-needed treatments at weeks 13 and 17. Primary outcome measure was the validated Western Ontario McMaster University Osteoarthritis Index (WOMAC). Secondary outcome measure was the validated Knee Pain Scale (KPS). Tertiary outcome measure was procedure-related pain severity and participant satisfaction. A total of 36 participants (60 +/- 8.7 years old, 21 females) with moderate-to-severe KOA received an average of 4.3 +/- 0.7 prolotherapy injection sessions over a 17-week treatment period and reported progressively improved scores during the 52-week study on WOMAC and KPS measures. Participants reported overall WOMAC score improvement 4 weeks after the first injection session (7.6 +/- 2.4 points, 17.2 %), and continued to improve through the 52-week follow-up (15.9 +/- 2.5 points, p < 0.001, 36.1 %). Knee Pain Scale scores improved in both injected (p < 0.001) and un-injected knees (p < 0.05). Prescribed low-dose opioid analgesia effectively treated procedure-related pain. Satisfaction was high and there were no adverse events. Female gender, age of 46 to 65 years old, and body-mass index of 25 kg/m(2) or less were associated with greater improvement on the WOMAC instrument. The authors concluded that in adults with moderate-to-severe KOA, dextrose prolotherapy may result in safe, significant, sustained improvement of knee pain, function, and stiffness scores. Moreover, they stated that randomized multi-disciplinary effectiveness trials including evaluation of potential disease modification are needed to further evaluate the effectiveness of prolotherapy for KOA.

Gross et al (2013) stated that although there has been a recent increase in interest regarding injectable therapy for non-insertional Achilles tendinosis, there are currently no clear treatment guidelines for managing patients with this condition. These investigators conducted a systematic review of clinical outcomes following injectable therapy of non-insertional Achilles tendinosis, identified patient-specific factors that are prognostic of treatment outcomes, provided treatment recommendations based on the best available literature, and identified knowledge deficits that require further investigation. They searched Medline (1948 to March week 1 2012) and EMBASE (1980 to 2012 week 9) for clinical studies evaluating the effectiveness of injectable therapies for non-insertional Achilles tendinosis. Specifically, they included RCTs and cohort studies with a comparative control group. Data abstraction was performed by 2 independent reviewers. The Oxford Level of Evidence Guidelines and GRADE recommendations were used to rate the quality of evidence and to make treatment recommendations. A total of 9 studies fit the inclusion criteria for the review, constituting 312 Achilles tendons at final follow-up. The interventions of interest included platelet-rich plasma (n = 54), autologous blood injection (n = 40), sclerosing agents (n = 72), protease inhibitors (n = 26), hemodialysate (n = 60), corticosteroids (n = 52), and prolotherapy (n =...
statistically significant effects of the treatment modalities, often studies revealed that certain injectables were no better than a placebo. The authors concluded that the literature surrounding injectable treatments for non-insertional Achilles tendinosis has variable results with conflicting methodologies and inconclusive evidence concerning indications for treatment and the mechanism of their effects on chronically degenerated tendons. They stated that prospective, randomized studies are needed in the future to guide Achilles tendinosis treatment recommendations using injectable therapies.

An UpToDate review on “iliotibial band syndrome” (Jackson, 2014) states that “Prolotherapy is the injection of irritants into or adjacent to tendons with the goal of inciting a healing response. This technique has not been the subject of controlled studies in ITBS”.

According to Martindale’s Extrapharmacopoeia, Sarapin is a brand name for an extract of the pitcher plant, or Sarracenia Purpurea. Martindale’s notes that “the roots and leaves of Sarracenia Purpurea have been used in the form of an aqueous distillate, administered by local injection, for neuromuscular or neuralgic pain.”

Sarapin is typically administered in conjunction with prolotherapy. There is inadequate evidence of the effectiveness of Sarapin for pain. One clinical study involving 180 patients found greater pain relief in patients administered facet blocks with Sarapin than those without (Manchikanti et al, 2000). Another study, using an animal model, found Sarapin to have no anesthetic effect (Harkins et al, 1997). Other studies found no effect of the addition of Sarapin on neural blockade (Manchikanti et al, 2004; Manchikanti et al, 2006; Manchikanti et al, 2007). Levin (2009) stated that injection of corticosteroid or Sarapin on the lumbar medial branch nerves is ineffective for the treatment of acute/subacute lumbo-sacral radicular pain.

Prolozone therapy is an injection technique similar to prolotherapy that uses ozone. According to the practitioners using this technique, the use of ozone causes the joint to heal much more quickly than in traditional prolotherapy because ozone is a highly reactive molecule and when injected into a joint capsule it is able to stimulate the fibroblastic joint repairing abilities.

**CPT Codes / HCPCS Codes / ICD-9 Codes**

**Other CPT codes related to the CPB:**

20550 Injection(s); single tendon sheath, or ligament, aponeurosis (e.g., plantar "fascia")

20600 - Arthrocentesis, aspiration and/or injection

20611

**HCPCS codes not covered for indications listed in the CPB:**

M0076 Prolotherapy [joint sclerotherapy and reconstructive ligament therapy]

**ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):**
Prolotherapy

524.60 - Temporomandibular joint disorders
524.69

718.00 - Other derangement of joint
718.99

724.2 - Lumbago

830.0, 830.1 - Dislocation of jaw

846.0 - 946.9 - Lumbosacral joint/ligament sprains and strains
847.2 - Lumbar sprains and strains

The above policy is based on the following references:


52. Jackson J. Iliotibial band syndrome. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed December 2014.
Copyright Aetna Inc. All rights reserved. Clinical Policy Bulletins are developed by Aetna to assist in administering plan benefits and constitute neither offers of coverage nor medical advice. This Clinical Policy Bulletin contains only a partial, general description of plan or program benefits and does not constitute a contract. Aetna does not provide health care services and, therefore, cannot guarantee any results or outcomes. Participating providers are independent contractors in private practice and are neither employees nor agents of Aetna or its affiliates. Treating providers are solely responsible for medical advice and treatment of members. This Clinical Policy Bulletin may be updated and therefore is subject to change.

CPT only copyright 2008 American Medical Association. All Rights Reserved.