Clinical Practice Guideline: **Prolotherapy**

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GUIDELINES

American Specialty Health – Specialty (ASH) considers prolotherapy as a treatment of musculoskeletal pain or any other indication unproven.

Despite ongoing studies, there continues to be insufficient evidence of its effectiveness in peer-reviewed literature.

For more information, see the *Techniques and Procedures Not Widely Supported as Evidence Based (CPG 133 – S)* clinical practice guideline.

HCPCS Code and Description

HCPCS Code	HCPC Code Description
M0076	Prolotherapy

Patients must be informed verbally and in writing the nature of any procedure or treatment technique that is considered experimental/investigational or unproven, poses a significant health and safety risk, and/or is scientifically implausible. If the patient decides to receive such services, they must sign a Member Billing Acknowledgment Form (for Medicare use Advance Beneficiary Notice of Non-Coverage form) indicating they understand they are assuming financial responsibility for any service-related fees. Further, the patient must sign an attestation indicating that they understand what is known and unknown about, and the possible risks associated with such techniques prior to receiving these services. All procedures, including those considered here, must be documented in the medical record. Finally, prior to using experimental/investigational or unproven procedures, those that pose a significant health and safety risk, and/or those considered scientifically implausible, it is incumbent on the practitioner to confirm that their professional liability insurance covers the use of these techniques or procedures in the event of an adverse outcome.

DESCRIPTION/BACKGROUND

Prolotherapy has its roots in an ancient practice used by Hippocrates in healing athletes. He found that by thrusting a hot lance into the injured athlete's joint that the scar tissue resulting from this procedure actually made the athletes stronger and perform better once they were healed. Modern prolotherapy evolved from an injection technique called sclerotherapy that arose in the 1920s to treat hernias and hemorrhoids. In the 1940s Dr. Earl Gedney, an osteopathic physician, began to use sclerotherapy for back related ailments. It was not until the 1950s that another physician coined the term prolotherapy. In modern practice sclerotherapy now refers to the use of injections to affect the venous system such as treatment for spider veins; while prolotherapy refers to injection for pain management and strengthening of joints and ligaments.

Prolotherapy is defined by the American Association of Orthopaedic Medicine (AAOM) as the injection of any substance(s) that promotes growth of normal cells, tissues, or organs. The most commonly used prolotherapy injection solutions contain dextrose; however, prolotherapy can apply to the injection of various substances. The AAOM outlines three different types of prolotherapy: growth factor injection prolotherapy, growth factor stimulation prolotherapy, and inflammatory prolotherapy. According to Rabago et al. (2011) prolotherapy is an injection-based complementary therapy for common chronic musculoskeletal conditions including tendinopathy, knee osteoarthritis, and low back pain. It involves the injection of irritant solutions into tender ligamentous and tendinous attachments and adjacent joint spaces. Prolotherapy is based on the premise that chronic musculoskeletal pain and disability often result from degeneration associated with these structures, and that prolotherapy addresses this degeneration at the tissue level. Although the mechanism of action for prolotherapy is not clearly understood, recent animal model studies reported that prolotherapy is associated with local inflammation, which may lead to induction of tissue growth factors. Prolotherapy injections may also act as central pain modulators.

One such substance used for pain management is the herbal formula known as Sarapin, which is a brand name for an extract of the pitcher plant, Sarracenia Purpurea. This plant is an alkaloid used in herbal and botanical medicine to treat stomach and renal complaints. Proponents of Sarapin's use in prolotherapy contend that its alkaloid properties lend it an analgesic effect when injected locally. Growth factor injection prolotherapy involves the injection of a growth factor (a complex protein) that specifically begins growth of a certain cell line. This type of prolotherapy is in the early stages of development and is currently being investigated as a treatment for arthritis. Growth factor stimulation prolotherapy involves the injection of a substance that causes the body to produce growth factors. Non-inflammatory dextrose is one example that has been examined in the treatment of various conditions of joint pain. Inflammatory prolotherapy involves the injection of a substance activating the inflammatory response to produce growth factors. These solutions may include dextrose but are designed to produce a more vigorous growth response. Examples include dextrose solutions of a concentration of 12%-25% and phenol-containing solutions. This has been examined to treat various types of joint pain, including back pain, neck pain, knee pain, and headache.

Although prolotherapy techniques and injected solutions vary by condition, clinical severity, and physician preferences, a core principle is that a small volume (0.2 to 0.5 mL) of solution is injected into tender ligamentous and tendinous attachments in a peppering fashion, and into adjacent joint spaces. The most common injectant is dextrose 15% (3 mL dextrose 50%, 5 mL saline 0.9%, and 2-mL lidocaine 2% [Xylocaine]); a similar volume of the sclerosant morrhuate sodium is also used. Treatment typically involves at least three injection sessions one month apart, but injection intervals vary from two to six weeks.

It is difficult to determine the safety profile of prolotherapy. It appears to be safe when applied by an experienced injector (Rabago et al., 2011), however studies often do not report adverse events consistently and therefore no conclusions can be drawn. The safety profile would include possible adverse and allergic reactions to a substance in the injecting solution and/or physical injury caused by the needle or other equipment used for the injection.

EVIDENCE REVIEW

Prolotherapy, also referred to as joint sclerotherapy or reconstructive ligament therapy, has been investigated as a treatment of various sources of musculoskeletal pain, including arthritis, chronic neck and back pain, degenerative disc disease, fibromyalgia, tendonitis, and ligamentous instability.

Musculoskeletal Pain

Systematic reviews concluded that there are limited high quality studies supporting the use of prolotherapy in the treatment of musculoskeletal pain or sport-related soft tissue injuries (Rabago et al., 2005; Kim et al., 2004; Uthman et al., 2003).

Hauser et al. (2016) completed a systematic review of dextrose prolotherapy for chronic musculoskeletal pain. Fourteen RCTs, 1 case-control study, and 18 case series studies met the inclusion criteria and were evaluated. Pain conditions were clustered into tendinopathies, osteoarthritis (OA), spinal/pelvic, and myofascial pain. The RCTs were high-quality Level 1 evidence (Physiotherapy Evidence Database ≥8) and found dextrose injection 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 low back pain. 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. Eighteen studies combined patient self-rating (subjective) with psychometric, imaging, and/or biomechanical (objective) outcome measurement and found both positive subjective and objective outcomes in 16 studies and positive objective but not subjective outcomes in two studies. All 15 studies solely using subjective or psychometric measures reported positive findings. Authors concluded that the use of dextrose prolotherapy is supported for treatment of tendinopathies, knee and finger joint OA, and spinal/pelvic pain due to ligament dysfunction. Efficacy in acute pain, as first-line therapy, and in myofascial pain cannot be determined from the literature.

Arias-Vázquez et al. (2024) identified and to analyzed the clinical studies that used subcutaneous injections of dextrose for treating musculoskeletal pain, in order to establish an overview. Twenty studies that met the criteria were included in this review; of those, 13 were randomized clinical trials, one non-randomized comparative study and six were case series studies, comprising a total of 1226 patients. In all included studies, efficacy in pain reduction was reported in the groups treated with dextrose when comparing evaluations at baseline, short term and medium term. Authors concluded that subcutaneous injections of dextrose could be a beneficial treatment for reducing musculoskeletal pain; however, factors such as the high heterogeneity in the treatment schemes, uncertainty in the mechanisms of action and the level of evidence found, indicate that this technique is still under development.

Low Back Pain

A California Technology Assessment Forum (CTAF) (Feldman, 2004) has concluded that prolotherapy does not meet CTAF's assessment criteria, as only one early study (Ongley, 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.

A systematic review found conflicting evidence regarding the effectiveness of prolotherapy injections for reducing pain and disability in patients with chronic low back pain (Yelland et al., 2004a). Conclusions were confounded by clinical heterogeneity among studies and by the presence of co-interventions. The authors found no evidence that prolotherapy injections alone were more effective than control injections alone. However, in the presence of co-interventions, prolotherapy injections were more effective than control injections, more so when both injections and co-interventions were controlled concurrently (Yelland et al., 2004a; Yelland et al., 2004c). A randomized controlled trial (RCT) evaluating the effectiveness of prolotherapy and exercise for patients with chronic nonspecific low back pain found no significant benefit for prolotherapy injections over normal saline injections but concluded that significant and sustained reductions in pain and disability occur with ligament injections, irrespective of the solution injected or the concurrent use of exercises (Yelland et al., 2004b).

A later critical review of the literature supporting prolotherapy found evidence that this technique may be effective for reducing spinal pain. Authors noted great variation among injection and treatment protocols used in the reviewed studies that precludes definite conclusions (Dagenais et al., 2005). An updated Cochrane review by Dagenais et al. (2007) stated that conflicting evidence exists for the efficacy of prolotherapy injections for patients with chronic low-back pain. When used alone, prolotherapy is not an effective treatment for chronic low-back pain. When combined with spinal manipulation, exercise, and other co-interventions, prolotherapy may improve chronic low-back pain and disability. Conclusions are confounded by clinical heterogeneity amongst studies and by the presence of co-interventions.

Watson and Shay (2010) performed a retrospective case series for patients with chronic low back pain involving ligamentous pathology receiving injection therapy. They concluded that at one year follow up, patients receiving prolotherapy using a variety of substances can be effective for some patients when performed by a skilled practitioner. Distal and Best (2011) completed a clinical review on the effectiveness of prolotherapy in the treatment of low back pain. Authors recognized that numerous studies do exist with the majority focusing on the treatment of low back pain. They conclude that there is a growing body of evidence to suggest that prolotherapy may be helpful in treating chronic low back pain when coupled with adjunctive therapies such as spinal manipulation or corticosteroid injections. They also note that prolotherapy may also be effective in treating chronic tendinopathies such as lateral epicondylosis and Achilles tendinopathy.

Giordano et al. (2021) aims to clarify the place of prolotherapy in chronic low back pain (CLBP) in a review article. A total of 12 articles was included in their present work. An area of agreement within these articles was that with consideration to the level of evidence and the quality of the studies assessed using the modified Coleman Score, prolotherapy is an effective management modality for CLBP patients in whom conservative therapies

failed. However, areas of controversy included that the presence of co-interventions and the clinical heterogeneity of the work confounds the overall conclusions. Authors concluded that the analysis of the studies included in the review, using appropriate tools, showed how their quality has decreased over the years, reflecting the need for appropriately powered well planned and performed randomized control trials.

Sacroiliac Joint Pain

In a small randomized controlled trial (*n*=48), Kim and colleagues (2010) evaluated the efficacy and long-term effectiveness of intra-articular prolotherapy compared with intra-articular steroid injection in relieving sacroiliac joint pain. Participants experienced sacroiliac joint pain (confirmed by greater than or equal to 50% improvement in response to local anesthetic block) lasting 3 months or longer and failed medical treatment. The treatment involved intra-articular dextrose water prolotherapy or triamcinolone acetonide injection using fluoroscopic guidance, with a biweekly schedule and maximum of 3 injections. Pain and disability scores were assessed at baseline, in 2 weeks, and monthly after completion of treatment. 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 ≥ 50% pain relief at 15 months was 58.7% in the prolotherapy group and 10.2% 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. However, further studies are needed to confirm the safety of the procedure and to validate an appropriate injection protocol.

In a retrospective cohort study, Hoffman and Agnish (2018) examined the effectiveness of sacroiliac (SI) joint prolotherapy for SI joint instability and characterized the patients most likely to benefit from this treatment. Patients referred for low back pain and diagnosed with SI joint instability received a series of three SI joint prolotherapy injections (15% dextrose in lidocaine) at approximately a one-month interval. The outcome of those completing treatment was retrospectively examined, and characteristics were compared between those with at least a minimum clinically important improvement and those without improvement. Results demonstrated that of 103 treated patients returning for post-treatment follow-up at a median of 117 days, 24 (23%) showed a minimum clinically important improvement despite a median of 2 years with low back pain and a mean (±SD) pre-intervention ODI of 54 ± 15 points. Much of the improvement was evident after the initial prolotherapy injection, and a 15-point improvement in ODI prior to the second prolotherapy injection had a sensitivity of 92% and specificity of 80% for determining which patients would improve. Authors concluded that a satisfactory proportion of patients with symptomatic SI joint instability as an etiology of low back pain can have clinically meaningful functional gains with prolotherapy treatment. The patients who are not likely to improve with

prolotherapy were generally evident by lack of improvement following the initial prolotherapy injection.

Enthesopathies

Wilkinson (2005) evaluated the effectiveness of injection therapy for enthesopathies. Thirty-five patients diagnosed as having painful enthesopathies as a major pain generator were studied. Of the patients studied, 86% of patients had undergone prior lumbar spine surgery and all were referred for neurosurgical evaluation for possible surgery. Patients were injected either with anesthetics alone or with anesthetics combined with phenol-glycerol proliferant prolotherapy. Patients received a total of 86 injections, 39 with local anesthetics, and 47 with prolotherapy. By clinical assessment patients obtained excellent to good relief of pain and tenderness after 80% of prolotherapy injections, but only 47% after anesthetics alone. By questionnaire, 66% reported excellent to good relief after prolotherapy vs. 34% after anesthetics alone. Patients reported improvement in work capacity and social functioning following both types of injections, but a greater reduction in focal pain intensity following prolotherapy injections. In the crossover portion of the study, patients reported that prolotherapy injections following initial anesthetic-only injections provided much better relief than that achieved after their anesthetic-only injections, and that anesthetic-only injections following initial prolotherapy injections failed to provide relief as good as that achieved after their prolotherapy. After this study, only 4 of 35 patients required additional spine surgery, but 29 of the 35 patients requested additional injections. Authors suggest that injection therapy can provide significant relief for back pain, even following a diagnosis of ‘failed back syndrome”. They continue to suggest that phenol-glycerol prolotherapy provides better and longer lasting relief than injection with anesthetics alone. Results should be considered with caution given the small sample size and other methodologic flaws.

Osteoarthritis

A randomized controlled trial (RCT) (n = 38 knees) evaluating the effectiveness of this technique for patients with knee osteoarthritis (OA) found that prolotherapy injection with 10% dextrose resulted in clinically and statistically significant improvements in knee OA. Preliminary blinded radiographic readings demonstrated improvement in several measures of OA severity. ACL laxity, when present, also improved (Reeves and Hassanein, 2000). Another RCT (n = 27) evaluating the effectiveness of this technique for patients with OA in finger joints found that dextrose prolotherapy was clinically effective and safe for the treatment of pain with joint movement and range limitation (Reeves and Hassanein, 2004). The use of prolotherapy was evaluated in a prospective, uncontrolled study of adults with at least 3 months of symptomatic moderate to severe knee osteoarthritis (Rabago et al., 2012). The primary objective of the study was to determine whether prolotherapy improved pain, stiffness, and function when compared to baseline status with 1-year follow-up. 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. The primary outcome measure was the Western Ontario McMaster University Osteoarthritis Index (WOMAC). Participants reported overall WOMAC score improvement 4 weeks after the first injection session (17.2%, 7.6 ± 2.4 points), and continued to improve through the 52-week follow-up (36.1%, 15.9 ± 2.5 points; $p<0.001$). Female gender, age 46-65 years old, and body mass index of 25 kg/m2 or less were associated with greater improvement on the WOMAC index. Limitations of this study include the lack of a randomized control group and the small number of study participants. Additional study with a larger randomized sample of participants is needed to determine the effectiveness of prolotherapy for knee osteoarthritis.

Rabago and colleagues (2013b) evaluated the efficacy of prolotherapy in adults with at least 3 months of painful knee osteoarthritis in a study supported by the National Center for Complementary and Alternative Medicine (NCCAM). A total of 90 participants were randomized to blinded injections (3 to 5 treatments with dextrose prolotherapy or saline) or at-home exercise. The study measures were limited to subjective responses to treatment, pain, stiffness, and functional limitations. All 3 groups showed improvements on the composite WOMAC, with significantly greater improvement in the prolotherapy group compared to saline and exercise groups. At 52 weeks, 50% of participants in the prolotherapy group achieved the minimum clinically important difference (MCID) of a 12-point change in WOMAC, compared to 30% of saline-treated participants and 24% of exercise participants. Knee pain scores also improved in the prolotherapy group. Limitations of this study include the relatively small sample size which resulted in an inability to detect uncommon adverse events such as intolerance to medication or rare-injection-related sequelae, lack of participants with very severe baseline WOMAC scores, and indirect assessment of participant satisfaction that was subject to bias. Rahimzadeh et al. (2014) compared the efficacy of three methods of intra-articular knee joint therapies with erythropoietin, dextrose, and pulsed radiofrequency. Seventy patients who were suffering from primary knee osteoarthrosis went through one of the treatment methods (erythropoietin, dextrose, and pulsed radiofrequency). The study was double-blind randomized clinical trial. Outcomes included pain, range of motion (ROM), and satisfaction. The authors concluded that intra-articular prolotherapy with erythropoietin was more effective in terms of pain level reduction and ROM improvement compared with dextrose and pulsed radiofrequency. Rabago et al. (2014) sought to determine whether injection with hypertonic dextrose and morrhuate sodium (prolotherapy) using a pragmatic, clinically determined injection schedule for knee osteoarthritis (KOA) results in improved knee pain, function, and stiffness compared to baseline status. They used a prospective three-arm uncontrolled study with 1-year follow-up. The participants were 38 adults who had at least 3 months of symptomatic KOA and who were in the control groups of a prior prolotherapy RCT (Prior-Control), were ineligible for the RCT (Prior-Ineligible) or were eligible but declined the RCT (Prior-Declined). The injection sessions occurred at 1, 5, and 9 weeks with as-needed treatment at weeks 13 and 17. Extra-articular injections of 15% dextrose and 5% morrhuate sodium were done at peri-articular tendon and ligament

insertions. The Prior-Declined group reported the most severe baseline WOMAC score (p=0.02). Compared to baseline status, participants in the Prior-Control group reported a score change of 12.4±3.5 points (19.5%, p=0.002). Prior-Decline and Prior-Ineligible groups improved by 19.4±7.0 (42.9%, p=0.05) and 17.8±3.9 (28.4%, p=0.008) points, respectively; 55.6% of Prior-Control, 75% of Prior-Decline, and 50% of Prior-Ineligible participants reported score improvement in excess of the 12-point minimal clinical important difference on the WOMAC measure. Post-procedure opioid medication resulted in rapid diminution of prolotherapy injection pain. Satisfaction was high and there were no adverse events. Authors concluded that prolotherapy using dextrose and morrhuate sodium injections for participants with mild-to-severe KOA resulted in safe, significant, sustained improvement of WOMAC-based knee pain, function, and stiffness scores compared to baseline status.

Eslamian and Amouzandeh (2015) sought to determine the therapeutic efficacy of dextrose prolotherapy on pain, range of motion, and function in patients with knee osteoarthritis (OA). In this prospective study, participants with symptomatic moderate knee osteoarthritis underwent prolotherapy with intra-articular injection of 20% dextrose water at baseline, and at 4 weeks and 8 weeks later. Patients were followed for 24 weeks. Pain severity, ROM, and Western Ontario and McMaster Universities arthritis index (WOMAC) scores were measured at baseline, 4, 8, and 24 weeks later. A total of 24 female patients (average age: 58.37 ± 11.8 years old) received 3-monthly injection therapies. The authors concluded prolotherapy with three intra-articular injections of hypertonic dextrose given 4 weeks apart for selected patients with knee OA, resulting in significant improvement of validated pain, ROM, and WOMAC scores, when baseline levels were compared at 24 weeks. Further studies with randomized controlled trials involving a comparison group are suggested to confirm these findings. Rabago et al. (2016) completed a qualitative assessment of patients receiving prolotherapy for knee osteoarthritis in a multimethod study. Randomized and open-label studies assessing prolotherapy for knee osteoarthritis have found quantitative improvement on the validated Western Ontario McMaster University Osteoarthritis Index (WOMAC) compared with baseline status and control therapies. This study assessed the qualitative response of participants receiving prolotherapy, an injection-based complementary treatment for symptomatic knee osteoarthritis (OA). Twenty-two patients treated with prolotherapy for symptomatic knee OA who were exited from three randomized and open-label studies participated. Most participants reported substantially improved knee-specific effects, resulting in improved quality of life and activities of daily living; four participants reported minimal or no effect. Clear, complete description of procedural rationale may enhance optimism about and adherence to treatment appointments.

Sit et al. (2016) conducted a systematic review with meta-analysis to synthesize clinical evidence on the effect of prolotherapy for knee OA. In the meta-analysis of two eligible studies, prolotherapy is superior to exercise alone by a standardized mean difference

(SMD) of 0.81, 0.78 and 0.62 on the WOMAC composite scale; and WOMAC function and pain subscale scores respectively. Moderate heterogeneity exists in all cases. Overall, prolotherapy conferred a positive and significant beneficial effect in the treatment of knee OA. Adequately powered, longer-term trials with uniform end points are needed to better elucidate the efficacy of prolotherapy. Hassan et al. (2017) completed another systematic review on the effectiveness of prolotherapy in treating knee OA in adults. Ten studies were evaluated, and results show significant improvement in scores for pain, function, and range of motion, both in the short term and long term. Patient satisfaction was also high in these patients (82%). Meta-analysis was not possible due to heterogeneity of outcome measures and populations. Authors conclude that moderate evidence suggests that prolotherapy is safe and can help achieve significant symptomatic control in individuals with OA. Future research should focus on larger sample size, standardization of treatment protocol and basic science evidence.

Krstičević et al. (2017) completed a systematic review on proliferative injection therapy for OA. They sought to systematically analyze RCTs about efficacy and safety of proliferative injection therapy (prolotherapy) for treatment of osteoarthritis (OA). Seven RCTs were included, with 393 participants aged 40-75 years and mean OA pain duration from three months to eight years. Follow-up was 12 weeks to 12 months. Studies analyzed OA of the knee joint ($n = 5$), first carpometacarpal joint ($n = 1$) and finger joints ($n = 1$). Various types of prolotherapy were used; dextrose was the most commonly used irritant agent. All studies concluded that prolotherapy was effective treatment for OA. No serious adverse events were reported. The studies had considerable methodological limitations. Authors concluded that limited evidence from low-quality studies indicates a beneficial effect of prolotherapy for OA management. The number of participants in these studies was too small to provide reliable evidence. Current data from trials about prolotherapy for OA should be considered preliminary, and future high-quality trials on this topic are warranted.

Rabago and Nourani (2017) completed a descriptive review on prolotherapy for OA and tendinopathy. The authors reviewed the basic science and clinical literature associated with prolotherapy for these conditions. Recent findings suggest that prolotherapy may be associated with symptom improvement in mild to moderate symptomatic knee osteoarthritis and overuse tendinopathy. Although the mechanism of action is not well understood and is likely multifactorial, a growing body of literature suggests that prolotherapy for knee osteoarthritis may be appropriate for the treatment of symptoms associated with knee osteoarthritis in carefully selected patients who are refractory to conservative therapy and deserves further basic and clinical science investigation for the treatment of osteoarthritis and tendinopathy.

Hassan et al. (2018) completed a systematic review on alternatives to biologics in management of knee osteoarthritis. A total of 18 studies were evaluated and results demonstrated moderate supporting evidence for prolotherapy.

Arias-Vázquez et al. (2019) evaluated the efficacy and safety of prolotherapy with hypertonic dextrose in patients with knee osteoarthritis. Ten randomized clinical trials were included in this systematic review, the total sample size comprised 328 patients treated with hypertonic dextrose prolotherapy (HDP) vs 348 controls treated with other infiltrations such as local anesthetics, hyaluronic acid, ozone, platelet-rich plasma, or interventional procedures like radiofrequency. In terms of pain reduction and function improvement, prolotherapy with hypertonic dextrose was more effective than infiltrations with local anesthetics, as effective as infiltrations with hyaluronic acid, ozone, or radiofrequency and less effective than PRP and erythropoietin, with beneficial effect in the short, medium, and long term. In addition, no side effects or serious adverse reactions were reported in patients treated with hypertonic dextrose. Although HDP seems to be a promising interventional treatment for knee OA, more studies with better methodological quality and low risk of bias are needed to confirm the efficacy and safety of this intervention.

Chen et al. (2022) assessed the effectiveness, compliance, and safety of dextrose prolotherapy for patients with knee osteoarthritis. Randomized controlled trials regarding the effectiveness of dextrose prolotherapy in knee osteoarthritis were identified. The included trials were subjected to meta-analysis. A total of 14 trials enrolling 978 patients were included in the meta-analysis. Compared with placebo injection and noninvasive control therapy, dextrose prolotherapy had favorable effects on pain, global function, and quality of life during the overall follow-up. Dextrose prolotherapy yielded greater reductions in pain score over each follow-up duration than did the placebo. Compared with other invasive therapies, dextrose prolotherapy generally achieved comparable effects on pain and functional outcomes for each follow-up duration. Subgroup results indicated that combined intra-articular and extra-articular injection techniques may have stronger effects on pain than a single intra-articular technique. Authors concluded that dextrose prolotherapy may have dose-dependent and time-dependent effects on pain reduction and function recovery, respectively, in patients with knee osteoarthritis. Due to remarkable heterogeneity and the risk of biases across the included trials, the study results should be cautiously interpreted.

Waluyo et al. (2023) evaluated the efficacy of dextrose prolotherapy (DPT) compared with other interventions in the management of osteoarthritis in a systematic review. Randomized controlled trials that compared the use of dextrose prolotherapy with other interventions (injection, placebo, therapy, or conservative treatment) in the treatment of osteoarthritis were included. Twelve studies reported that DPT was as effective or even more effective in improving functional outcomes compared with other interventions whilst others found

that HA, PRP, EP, and ACS were more effective. Fourteen studies assessed the effectiveness of DPT and ten of them reported that DPT was more effective in reducing pain compared with other interventions. Authors concluded that dextrose prolotherapy in osteoarthritis confers potential benefits for pain and functional outcomes, but this systematic review found that the studies to date are at high risk of bias.

Lateral Epicondylosis/Epicondylitis

A pilot RCT (*n* = 24) evaluating the effectiveness of this technique in patients with lateral epicondylosis found that prolotherapy with dextrose sodium morrhuate was well-tolerated, effectively decreased elbow pain, and improved strength testing when compared to control group saline injections (Scarpone et al., 2008). A systematic review by Rabago et al. (2009) concluded that there is strong pilot-level evidence supporting the use of prolotherapy, polidocanol, autologous whole blood and platelet-rich plasma injections in the treatment of lateral epicondylosis, and that more rigorous studies are needed to determine long-term effectiveness and safety. Krogh et al. (2013) performed a systematic review and meta-analysis of the available randomized trials, concluding there was "a paucity of evidence from unbiased trials on which to base treatment recommendations regarding injection therapies for the treatment of lateral epicondylitis."

Rabago and colleagues (2013a) conducted a randomized controlled trial of 26 adults (32 elbows) with chronic lateral epicondylosis for 3 months or longer who were randomized to ultrasound-guided prolotherapy with dextrose solution, ultrasound-guided prolotherapy with dextrose-morrhuate sodium solution, or watchful waiting. The primary outcome was the Patient-Rated Tennis Elbow Evaluation (100 points) at 4-, 8-, and 16 weeks (all groups) and at 32 weeks (prolotherapy groups). The participants receiving prolotherapy with dextrose and prolotherapy with dextrose-morrhuate reported improvement at 4-, 8-, and/or 16 weeks compared with those in the wait-and-see group ($p<0.05$). The grip strength of the participants receiving prolotherapy with dextrose exceeded that of the prolotherapy with dextrose-morrhuate and the watchful waiting group at 8 and 16 weeks ($p<0.05$). Limitations in drawing conclusions from this pilot study include the small number of participants and the lack of blinding.

Kahlenberg et al. (2015) discussed prolotherapy in their article on new developments in the use of biologics and other modalities in the management of lateral epicondylitis. They describe it as such: prolotherapy for lateral epicondylitis includes multiple injections of a small amount of irritant or sclerosing solution over the course of a two-week trial. Commonly used irritants include hypertonic dextrose, phenol-glycerine-glucase, or sodium morrhuate. The proposed mechanism of prolotherapy injections is that the hypertonic dextrose causes cell rupture through osmosis while the monosodium morrhuate attracts inflammatory mediators and improves blood supply to the diseased tendon. They describe research by Scarpone and colleagues who performed a randomized controlled trial comparing prolotherapy consisting of hypertonic dextrose and sodium morrhuate versus

placebo for lateral epicondylitis. A series of 3 separate injections were performed over 8 weeks and those patients in the prolotherapy group had significantly improved pain scores and isometric strength at 16 weeks compared to placebo. No long-term data suggests that prolotherapy allows for better pain relief and function compared to placebo and further long-term follow-up studies are needed for better recommendations. Yelland et al. (2019) compared the short- and long-term clinical effectiveness, cost effectiveness, and safety of prolotherapy used singly and in combination with physiotherapy for lateral epicondylalgia. Using a single-blinded randomized clinical trial design, 120 participants with lateral epicondylalgia of at least 6 weeks' duration were randomly assigned to prolotherapy (4 sessions, monthly intervals), physiotherapy (weekly for 4 sessions) or combined (prolotherapy+physiotherapy). The Patient-Rated Tennis Elbow Evaluation (PRTEE) and participant global impression of change scores were assessed by blinded evaluators at baseline, 6, 12, 26 and 52 weeks. Eighty-eight percent completed the 12-month assessment. At 52 weeks, there were substantial, significant improvements compared with baseline status for all outcomes and groups, but no significant differences between groups. The physiotherapy group exhibited greater reductions in PRTEE at 12 weeks than the prolotherapy group ($p = 0.014$).

Zhu et al. (2022) systematically reviewed the effectiveness of hypertonic dextrose prolotherapy (DPT) on pain intensity and physical functioning in patients with lateral elbow tendinosis (LET) compared with other active non-surgical treatments. The search identified 245 records; data from 8 studies (354 patients) were included. Pooled results favored the use of DPT in reducing tennis elbow pain intensity compared with active controls at 12 weeks post-enrollment. Pooled results also favored the use of DPT on physical functioning compared with active controls at 12 weeks, with Disabilities of the Arm, Shoulder and Hand scores achieving a mean difference of -15.04 and of low heterogeneity. No major related adverse events have been reported. Authors concluded that DPT is superior to active controls at 12 weeks for decreasing pain intensity and functioning by margins that meet criteria for clinical relevance in the treatment of LET. Although existing studies are too small to assess rare adverse events, for patients with LET, especially those refractory to first-line treatments, DPT can be considered a nonsurgical treatment option in carefully selected patients. Further high-quality trials with comparison with other injection therapies are needed.

Lower Limb Tendinopathy

Sanderson and Bryant (2015) studied the effectiveness and safety of prolotherapy injections for management of lower limb tendinopathy and fasciopathy in a systematic review. The aim of this review was to identify and evaluate existing research to determine the clinical effectiveness and safety of prolotherapy injections for treatment of lower limb tendinopathy and fasciopathy. All prospective randomized and non-randomized trials, cohort studies, case-series, cross-sectional studies, and controlled trials assessing the effectiveness of one or more prolotherapy injections for tendinopathy or fasciopathy at or

below the superior aspect of the tibia/fibula were included. Two hundred and three studies were identified, eight of which met the inclusion criteria. These were then grouped according to tendinopathy or fasciopathy being treated with prolotherapy injections: Achilles tendinopathy, plantar fasciopathy and Osgood-Schlatter disease. The methodological quality of the eight included studies was generally poor, particularly in regard to allocation concealment, intention to treat analysis and blinding procedures. Results of the analysis provide limited support for the hypothesis that prolotherapy is effective in both reducing pain and improving function for lower limb tendinopathy and fasciopathy, with no study reporting a mean negative or non-significant outcome following prolotherapy injection. The analysis also suggests prolotherapy injections provide equal or superior short-, intermediate-and long-term results to alternative treatment modalities, including eccentric loading exercises for Achilles tendinopathy, platelet-rich plasma for plantar fasciopathy and usual care or lignocaine injections for Osgood-Schlatter disease. No adverse events following prolotherapy injections were reported in any study in this review. The results of this review found limited evidence that prolotherapy injections are a safe and effective treatment for Achilles tendinopathy, plantar fasciopathy and Osgood-Schlatter disease, however more robust research using large, methodologically-sound randomized controlled trials is required to substantiate these findings.

An RCT (*n* = 43) evaluating the effectiveness of eccentric loading exercises (ELE) and prolotherapy for treatment of painful Achilles tendinosis found that ELE combined with prolotherapy resulted in more rapid improvements than ELE alone (Yelland et al., 2010). Yelland and colleagues (2011) reported a multicenter randomized trial of prolotherapy or exercises for Achilles tendonitis in 43 individuals. The percentage of individuals achieving full recovery 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 individuals 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 individuals showing recovery. Additional randomized trials are needed to confirm findings. Choi et al. (2011) concluded that the available literature evaluating 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. Gross and colleagues (2013) conducted a systematic review of clinical outcomes following injectable therapy of non-insertional Achilles tendinosis. The nine clinical studies that met the inclusion criteria at the final follow-up consisted of randomized controlled trials and cohort studies with a comparative control group (n=312 Achilles tendons). Interventions 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*=20).

Morath et al. (2018) studied the effect of sclerotherapy and prolotherapy on chronic painful Achilles tendinopathy (AT) in a systematic review including meta-analysis. After screening articles, 18 articles were available for qualitative synthesis, six of which were subjected to meta-analysis. Four RCTs were ranked as having a low risk of selection bias. Three of those reported a statistically significant drop in the visual analog scale (VAS) score, one reported a significant increase in the VISA-A Score. Twelve of thirteen human studies reported positive results in achieving pain relief and patient satisfaction, whereas only one study's finding differed. Meta-analysis revealed an unambiguous result in favor of the intervention. Authors concluded that this systematic review suggests that these interventions may be effective treatment options for AT and that they can be considered safe given the low number of adverse events. However, long-term studies and RCTs are still needed to support their recommendation.

Rotator Cuff Tendinopathy

Lin et al. (2019) compared the effectiveness of diverse injections in patients with rotator cuff tendinopathy. Among the 1495 records screened, 18 studies were included in the meta-analysis. The primary outcome was pain reduction, and the secondary outcome was functional improvement. Results determined that for patients with rotator cuff tendinopathy, corticosteroid plays a role in the short term (3-6wk) but not in long-term (over 24wk) pain reduction and functional improvement. By contrast, PRP and prolotherapy may yield better outcomes in the long term (over 24wk). On account of heterogeneity, interpreting these results with caution is warranted.

Catapano et al. (2020) systematically reviewed and evaluated the efficacy and complication profile of prolotherapy using hyperosmolar dextrose solution injection for rotator cuff tendinopathy. Five studies satisfied inclusion criteria. Included studies analyzed a total of 272 participants with a final follow-up ranging from 6 weeks to 12 months. Prolotherapy differed greatly among studies. There was statistically significant improvement in pain intensity with multisite injection protocols compared to physical therapy and medical management in both studies. Ultrasound-guided supraspinatus injection trials did not find any statistically significant difference in pain intensity, range of motion, strength, function, or ultrasound characteristics compared to controls of enthesis saline injection or corticosteroid. The complication rate was low, with only 6/272 participants experiencing adverse events consisting of transient increase in pain for 1 to 2 days postintervention. Authors concluded that prolotherapy with hyperosmolar dextrose solution is a potentially effective adjuvant intervention to physical therapy for patients with rotator cuff tendinopathy ranging from tendinosis to partial-thickness and small full-thickness tears. Further studies are necessary to determine effects in subpopulations as well as optimal technique including dextrose concentration, volume, and location.

Zhang et al. (2024) evaluated the efficacy of hypertonic glucose proliferation therapy in the treatment of rotator cuff problems. Meta-analysis finally contained 6 papers. In six

investigations, the test and control group's VAS scores improved, with the test group score considerably outperforming the control group, shoulder pain and disability index (SPADI) score, flexion, abduction, internal rotation, and external rotation. Authors concluded that the findings of this study suggest that individuals with rotator cuff injuries may benefit from hypertonic dextrose proliferation treatment based on the visual analogue scale (VAS) score, the Shoulder Pain and Disability Index (SPADI) score, flexion, & abduction. These results must, nevertheless, be supported by high-caliber follow-up research.

Temporomandibular Joint

Reeves et al. (2016) state in their narrative review of prolotherapy that data on effectiveness for temporomandibular dysfunction are promising but insufficient for recommendations. Nagori et al. (2018) analyzed the available evidence in order to assess the efficacy of dextrose prolotherapy in improving outcomes in temporomandibular joint (TMJ) hypermobility patients as compared to placebo. Within the limitations of the study, dextrose prolotherapy may cause significant reduction in mouth opening and pain associated with TMJ hypermobility. Authors stated there is a need of more high-quality RCTs with larger sample size and homogenous prolotherapy protocol to draw stronger conclusions on the effect of dextrose prolotherapy in patients with TMJ hypermobility. Louw et al. (2019) assessed the efficacy and longer-term effectiveness of dextrose prolotherapy injections in participants with temporomandibular dysfunction. Based on results, intra-articular dextrose injection (prolotherapy) resulted in substantial improvement in jaw pain, function, and MIO compared with masked control injection at 3 months; clinical improvements endured to 12 months.

Sit et al. (2021) conducted a systematic review with meta-analysis of randomized controlled trials (RCTs) to synthesize evidence on the effectiveness of Hypertonic dextrose prolotherapy (DPT) for temporomandibular disorders (TMDs). Eleven electronic databases were searched from their inception to October 2020. The primary outcome of interest was pain intensity. Secondary outcomes included maximum inter-incisal mouth opening (MIO) and disability score. Ten RCTs (n = 336) with some to high risk of bias were included. In a meta-analysis of 5 RCTs, DPT was significantly superior to placebo injections in reducing TMJ pain at 12 weeks, with moderate effect size and low heterogeneity. No statistically significant differences were detected for changes in MIO and functional scores. In this systematic review and meta-analysis, evidence from low to moderate quality studies show that DPT conferred a large positive effect which met criteria for clinical relevance in the treatment of TMJ pain, compared with placebo injections.

Osteitis Pubis

Choi et al. (2011) evaluated the most current evidence in a systematic review of treatment options for 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. Treatment options included either conservative measures/physical

therapy, local injection with corticosteroids and/or local anesthetic, dextrose prolotherapy, surgery or antibiotic therapy. There were no randomized controlled trials available for review. Only one case series described the use of dextrose prolotherapy as a treatment modality. The authors concluded that the evidence was weak in all case reports/case series and suggested further study is necessary to compare the different treatment options and determine which modality provides the fastest return to sport. Yelland et al. (2011) was the only prolotherapy study included in the review.

Plantar Fasciitis/Connective Tissue

Chung et al. (2020) assessed the effectiveness and superiority of prolotherapy separately in treating dense fibrous connective tissue injuries. Ten trials involving 358 participants were included for review. At study level, the majority of comparisons did not reveal significant differences between dextrose prolotherapy and no treatment (or placebo) regarding pain control. The meta-analysis showed dextrose prolotherapy was effective in improving activity only at immediate follow-up (i.e., 0-1 month); and superior to corticosteroid injections only in pain reduction at short-term follow-up (i.e., 1-3 month). Authors concluded that there is insufficient evidence to support the clinical benefits of dextrose prolotherapy in managing dense fibrous tissue injuries. More high-quality randomized controlled trials are warranted to establish the benefits of dextrose prolotherapy.

Lai et al. (2021) Dextrose prolotherapy (DPT) aimed to evaluate the effectiveness and safety of DPT for plantar fasciitis. Six studies with 388 adult patients diagnosed with plantar fasciitis were included for the meta-analysis. In terms of pain scores improvement, DPT was superior to placebo or exercise in the short-term and the medium-term. DPT was inferior to corticosteroid injection in the short-term. For functional improvement, DPT was superior to placebo or exercise in the short-term, but inferior to corticosteroid injection and extracorporeal shock wave therapy in the short-term. Randomized controlled trials showed a better pain improvement in the long-term for patients treated with DPT compared to corticosteroid ($P = .002$) and exercise control ($P < .05$). No significant differences were found between patients treated with DPT and patients treated with platelet-rich plasma. Authors concluded that dextrose prolotherapy was a safe and effective treatment option for plantar fasciitis that may have long-term benefits for patients. The effects were comparable to extracorporeal shock wave therapy or platelet-rich plasma injection. Further studies with standardized protocols and long-term follow-up are needed to address potential biases.

Chutumstid et al. (2023) systematically investigated the efficacy and safety of dextrose prolotherapy for treating chronic plantar fasciitis. Comprehensive review of randomized controlled trials investigating dextrose prolotherapy for chronic plantar fasciitis was done. The changes in visual analog scale (VAS) pain score, foot function index (FFI), American Orthopaedic Foot and Ankle Society (AOFAS) score, and plantar fascia thickness were analyzed. Reports of complications of the procedure were collected. Eight randomized

controlled trials (RCTs) were included in the meta-analysis, analyzing 444 patients in total. The subgroup analysis showed that at short-term follow-up (<6 months) dextrose prolotherapy was more effective in reducing VAS pain score compared to the non-active treatment control group including exercise and normal saline solution (NSS) injection. However, there was no difference in the change of VAS pain score between dextrose prolotherapy and active treatment control group, which included extracorporeal shock wave therapy (ESWT), steroid injection, and platelet-rich plasma (PRP) injection. Dextrose prolotherapy was more effective in reducing FFI, increasing AOFAS score, and reducing plantar fascia thickness at short-term (<6 months) follow-up compared to other comparators. For long-term (≥6 months) follow-up, there was no significant difference in the change in VAS pain score and FFI between the dextrose prolotherapy group and other comparators. No serious complication was reported. Authors concluded that dextrose prolotherapy is an effective treatment of chronic plantar fasciitis to reduce pain, improve foot functional score, and decrease plantar fascia thickness at short-term follow-up. Further studies in larger populations are needed to identify the optimal treatment regimen including dextrose concentration, volume, injection site, injection technique, and the number of injections required. The long-term effects of these treatments also require further examination.

Ahadi et al. (2023) investigated the effect of dextrose prolotherapy (DPT) versus placebo/other non-surgical treatments on pain in chronic plantar fasciitis. The primary outcome was pain, and the secondary outcomes were foot function and plantar fascia thickness. Overall, eight studies with a total of 449 patients were included in the meta-analysis. All the studies included reported short-term pain. A large effect size was observed favoring the use of DPT to reduce pain in patients with chronic plantar fasciitis in the short-term. The results for foot function improvement and plantar fascia thickness reduction in the short-term were also in favor of DPT. Authors concluded that since almost all the included studies had high risk of bias and multiple trials lacked long-term follow-ups, further high-quality research is required to determine the long-term effects of DPT vs placebo/other non-surgical interventions.

Fong et al. (2023) reviewed the effectiveness of hypertonic dextrose prolotherapy (DPT) in plantar fasciopathy (PF) compared with other non-surgical treatments. Eight RCTs (*n*=469) met the inclusion criteria. Pooled results favored the use of DPT versus normal saline (NS) injections in reducing pain and improving function in the medium term. Pooled results also showed corticosteroid (CS) injections were superior to DPT in reducing pain in the short term. Authors concluded that low certainty evidence demonstrated that DPT was superior to NS injections in reducing pain and improving function in the medium term, but moderate certainty evidence showed that it was inferior to CS in reducing pain in the short term. Further high-quality RCTs with standard protocol, longer-term follow-up, and adequate sample size are needed to confirm its role in clinical practice.

All Musculoskeletal Conditions

Hsu et al. (2023) completed a narrative review of mechanisms, techniques, and protocols, and evidence for common musculoskeletal conditions. Authors suggested that prolotherapy is beneficial in a variety of different musculoskeletal conditions, including, but not limited to, lateral epicondylosis, rotator cuff tendinopathy, plantar fasciitis, Achilles tendinopathy, osteoarthritis, low back pain, sacroiliac joint pain, and TMJ laxity.

No research or evidence was found on the usage of herbal solutions such as Sarapin in the literature. As such, ASH clinical committees were unable to evaluate the effectiveness and safety of injecting herbal solutions.

PRACTITIONER SCOPE AND TRAINING

Practitioners should practice only in the areas in which they are competent based on their education, training, and experience. Levels of education, experience, and proficiency may vary among individual practitioners. It is ethically and legally incumbent on a practitioner to determine where they have the knowledge and skills necessary to perform such services and whether the services are within their scope of practice.

It is best practice for the practitioner to appropriately render services to a member only if they are trained, equally skilled, and adequately competent to deliver a service compared to others trained to perform the same procedure. If the service would be most competently delivered by another health care practitioner who has more skill and training, it would be best practice to refer the member to the more expert practitioner.

Best practice can be defined as a clinical, scientific, or professional technique, method, or process that is typically evidence-based and consensus driven and is recognized by a majority of professionals in a particular field as more effective at delivering a particular outcome than any other practice (Joint Commission International Accreditation Standards for Hospitals, 2020).

Depending on the practitioner's scope of practice, training, and experience, a member's condition and/or symptoms during examination or the course of treatment may indicate the need for referral to another practitioner or even emergency care. In such cases it is prudent for the practitioner to refer the member for appropriate co-management (e.g., to their primary care physician) or if immediate emergency care is warranted, to contact 911 as appropriate. See *Managing Medical Emergencies (CPG 159 – S)* clinical practice guideline for information.

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