# Chapter 6
# Prolotherapy


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## Introduction

When practitioners use the term prolotherapy, they refer to an injection of a solution meant to rehabilitate an incompetent structure, usually by means of promoting sclerosis at the injection site [1]. It is identified as a regenerative injection therapy but differs from modern regenerative therapies such as platelet-rich plasma (PRP) and stem cell therapies because it lacks a biologic agent [2]. Hypertonic dextrose is the most commonly used prolotherapy solution and is popular in the United States and internationally. It is an inexpensive regenerative therapy option that results in great accessibility [3]. One of the earliest reports of prolotherapy for the musculoskeletal system was published in 1956 by GS Hackett, who reported that the treatment resulted in the proliferation of cells to strengthen injected tissues [4]. The most commonly used injectate is hyperosmolar dextrose (usually 10–30%) [5, 6]. This technique has been used for over 100 years [3] and many different solutions have been used to create similar effects, including phenol-glycerine-glucose (no longer used, but commonly studied previously) and sodium morrhuate (used currently, but less often than hyperosmolar glucose) [7]. Injection protocols are also varied but typically involve repeated injections on a weekly basis over several months. Anti-inflammatory medications are generally avoided after the injections to promote the expected controlled inflammatory response. Regular activity is typically resumed after resolution of possible post-injection inflammation [3].

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## Mechanism of Action

The mechanism of action of prolotherapy is unclear but there have been several demonstrated effects of dextrose on cytokines in vitro. Currently discussed mechanisms include the induction of an inflammatory reaction that stimulates the wound-healing process by attracting growth factors and inducing vascular sclerosis [4, 8]. GLUT 1–4 proteins are cell surface transporters of dextrose that transport glucose into human cells and interact with cytokines to signal cell growth or repair [9]. Glucose and other sugar exposures to cells have demonstrated increased genetic expression of mesangial cell activation regulators including connective tissue growth factor (CTGF) by way of increased expression of transforming growth factor β1 (TGF- β1) and stimulating protein kinase C-dependent pathways [10]. These cytokine pathways are linked to increased production of fibroblasts [10, 11], chondrocytes [12, 13], and nerve cells in animal and human cells [14, 15].

An alternative proposed mechanism suggests that hyperosmolar dextrose opens potassium channels and thus hyperpolarizes nerve cells. This in turn decreases perceived pain by way of inhibited nociceptive fibers [8]. Another alternate mechanism suggests hyperosmolar dextrose slows osteoarthritis progression and improves cartilage regeneration, as demonstrated by multiple animal studies with small sample sizes [7, 8].

## Effects of Prolotherapy on Ligaments and Tendons In Vitro and in Animal Studies

The response of tissues to prolotherapy has been studied in the rat medial collateral ligament (MCL). The results showed leukocyte and macrophage infiltration initially after prolotherapy treatment when compared to placebo, saline injections, or dry needling. This inflammatory response is hypothesized to reduce pain by limiting excessive neovascularization and neural ingrowth in the case of tendinopathy. However, the inflammatory response reported in the above MCL study varied between different prolotherapy injections [3, 16]. In the thigh muscles of guinea pigs, Harris and White demonstrated that prolotherapy induced white blood cell infiltration at 6 hours post-injection, marked edema at 24 hours post-injection, and finally the recruitment of large undifferentiated cells and fibroblasts after 24 hours [17]. Another study by Harris et al. demonstrated that within 10 months after the treatment, the thigh muscles underwent necrosis and were walled off by fibrous tissue and the necrotic tissue was then replaced entirely by thick bands of fibrous tissue [16].

The studies of the murine MCL demonstrated another interesting finding, an increase in the MCL cross-sectional area after prolotherapy. This suggests another

mechanism of pain relief related to structural changes in treated tissues. However, in these studies, there were no changes in strength, stiffness, or laxity of the treated ligaments [16]. Separate work by Liu et al. on rabbit MCL did however demonstrate increased junctional strength, in addition to increased ligamentous mass, cross-sectional area, and thickness [18].

Other groups have similarly reported that the injection of sodium morrhuate into rabbit patellar and Achilles tendons increases their diameters [19]. Still others have reported increased strength in the patellar tendons of rats after prolotherapy, giving credence to the hypothesis that structural changes are responsible for the pain relief effect of prolotherapy. These results should be interpreted with caution, however, as a similar study by Harrison in murine Achilles tendons showed no difference in tendon tensile strength after injections with 18.5% dextrose compared to no intervention [19].

In conclusion, the mechanism of pain control mediated by prolotherapy at the tissue level is not well understood. It is likely multifactorial and due to both tissue displacement effects of the needle and effects of the injectate.

## Osteoarthritis Clinical Studies

Osteoarthritis (OA) represents one of the most prevalent and financially burdensome health conditions worldwide; it is the fastest growing form of disability [20]. Treatment options are limited and, short of arthroplasty, typically only provide temporary relief. Prolotherapy has historically been used to address elements of laxity and instability within soft and connective tissue structures such as ligament and tendon, on the basis of increased tendon diameter, ligament hypertrophy, fibrosis, and tensile strength observed following direct injection of pro-inflammatory agents into these tissues. However, more recent research, most occurring within the twenty-first century, has sought to address whether these same prolotherapeutic injectates can address healing and/or ultimately confer anti-inflammatory effects within other tissues and regions of the musculoskeletal system—more specifically, within joints to address symptomatic osteoarthritis.

Overwhelmingly, the existing research examining this topic is limited in scope and study size and is not without methodological flaws. However, the existing body of literature suggests that intra-articular injection of prolotherapeutic injectate into symptomatic osteoarthritic joints, ranging from the small joints of the hand to large joints such as the knee, may be supported by mild to moderate evidence. The studies generally support positive effects of prolotherapy on joint pain, joint stiffness symptoms, and improvement on disability and quality of life.

## *Prolotherapy Effects on Small Joints*

Research on prolotherapy treatment for osteoarthritis dates back to the early 2000s with small studies examining the use of 10% dextrose solution in MCP, PIP, and DIP joints of the hand [21]. Reeves and Hassanein randomized 27 patients with symptomatic hand OA for at least 6 months to either an intervention group ($n = 13$) or control group ($n = 14$). Injections were performed at 0, 2, and 4 months, with evaluation at 6 months post-initial injection. The intervention group saw a statistically significant improvement in pain with finger movement and flexion range of motion; this group also reported less pain at rest and demonstrated better grip strength; however, these latter two metrics were not statistically significant.

## *Prolotherapy Effects on Knee Osteoarthritis*

Intrigued, this same group led by Reeves and Hassanein went on to examine the effects of dextrose injections to the knee [22]. Thirty-eight patients were selected who demonstrated at least 6 months of knee pain along with Kellgren-Lawrence radiographic evidence of knee OA. These participants were randomized into two groups: an intervention group, which underwent three injections, spaced out every 2 weeks, of a 10% dextrose/0.075% lidocaine solution, and a control group, which received an identical control solution absent the 10% dextrose. The dextrose-treated participants also underwent three further injections every 2 weeks of the 10% dextrose solution. Again, at 6 months of follow-up from the first injection, those who received the dextrose injections reported statistically significant less knee pain, swelling, buckling episodes, and greater knee flexion range of motion when compared with controls. These effects persisted at a 12-month follow-up. Secondary analysis revealed that 8 out of 13 knees treated with dextrose initially showed clinically significant ACL laxity which subsequently improved with decreased laxity at 12 months of follow-up.

Research into the use of prolotherapy in subsequent years focused primarily again on soft tissues, with a return in interest in the experimental use of prolotherapy for OA in the early 2010s. In 2012, Rabago and Patterson [23] identified 36 adults with moderate to severe knee OA and symptoms for at least 3 months; all participants received both extra-articular injections of 15% dextrose and intra-articular injections of 25% dextrose at 1, 5, and 9 weeks, with additional "as-needed" injections at weeks 13 and 17. Over 1 year of follow-up, participants reported progressively improved scores on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and the validated Knee Pain Scale (KPS). Score improvement was observed as early as 4 weeks post-initial injection and demonstrated continued improvement in both measures over the 1 year of follow-up. Greater improvement was statistically significantly related to female gender, younger age (45–65 years), and BMI <25 kg/m$^2$. While promising, this study was severely limited methodologically by its single-arm, uncontrolled design, as well as the confounding nature

associated with injecting both intra-articularly and extra-articularly. In 2013, the same group returned to the subject to perform a three-arm, blinded, randomized controlled trial [24]. Ninety adults with at least 3 months of knee OA were randomized to injection (dextrose versus saline) or a home exercise program. Again, both extra- and intra-articular injections were performed, at 1, 5, and 9 weeks. At 1 year of follow-up, all groups reported statistically significant improvements in composite WOMAC scores compared with baseline. When adjusting for sex, age, and BMI, WOMAC scores for patients receiving the dextrose injections improved significantly more, exceeding the WOMAC-based minimal clinically important difference. Individual knee pain scores also improved statistically significantly more in the prolotherapy group.

Rabago went on to attempt to further characterize the possible mechanism underlying these observed effects. In 2013, Rabago et al. examined both knee OA-specific quality of life and intra-articular cartilage volume in patients treated with intra-articular prolotherapy [25]. Knee-specific quality of life improved significantly among knee OA participants who received monthly knee prolotherapy injections over 5 months as compared with controls. Interestingly, when examining radiographic progression of knee articular cartilage degradation over time (via MRI), both groups saw interval decrease in knee articular cartilage over 1 year at about the same rate; however, the prolotherapy recipients who lost the least cartilage volume also had the greatest improvement in pain scores. Authors noted that among these participants, the change in cartilage volume and knee pain (but not stiffness or function) scores were correlated, with each 1% of cartilage volume loss being associated with 2.7% less improvement in pain score.

In 2014, Hauser et al. retrospectively evaluated the effects of both intra-articular and extra-articular knee prolotherapy injections on pain, stiffness, crepitus, and improvements in physical activity levels in 69 patients with chondromalacia patella [26]. Patients received, at one visit, 24 injections of 15% dextrose, 0.1% procaine, and 10% sarapin (total 40 cc) in the anterior knee at various locations: MCL and LCL, patellar ligament, vastus medialis and iliotibial tract, and pes anserinus, with 8 cc injected intra-articularly. Six weeks following the last injection, patients reported a statistically significant decrease in pain at rest, during ADLs, and with exercise. These patients also reported a significant decrease in stiffness and crepitus and increase in knee range of motion.

A case series performed in 2016 by Topol et al. sought to better understand if dextrose does in fact exert a chondrogenic effect to explain some of the clinical effects observed with prolotherapy injected into the joint space. Six participants with symptomatic knee OA for at least 6 months and arthroscopically confirmed medial compartment exposed subchondral bone were treated with four to six monthly 10 mL intra-articular knee injections with 12.5% dextrose. Knee articular cartilage was examined both pre-injection and at 8 months post-injection, via direct visualization (arthroscopic examination of nine standardized medial condyle zones) and biopsy of a cartilage growth area. Fifty-four total zones were examined (9 zones over 6 participants); in 19 of these, blinded arthroscopy readers reported evidence of cartilage growth post-treatment as compared with pre-treatment. Biopsy specimens showed

metabolically active cartilage, with parallel fibers and cartilage typing patterns consistent with both fibrocartilage and hyaline cartilage. Additionally, compared with baseline, median WOMAC scores statistically significantly improved by 13 points [27].

## *Intra-articular Prolotherapy Treatment Versus Corticosteroid and Platelet-Rich Plasma Treatments*

Several other groups have attempted to compare intra-articular dextrose injections with other agents, such as platelet-rich plasma (PRP) or corticosteroid. In 2014, Jahangiri et al. compared the use of hypertonic dextrose with corticosteroid for the treatment of first carpometacarpal joint OA in a randomized controlled trial [28]. Sixty patients with both symptomatic and radiographic first CMC osteoarthritis were randomized to a corticosteroid injection group ($n$ = 30, received 2 monthly saline placebo injections followed by a single dose of 40 mg methylprednisolone acetate) or a prolotherapy group ($n$ = 30, 20% dextrose and 2% lidocaine solution performed monthly for 3 months). At 1-month post-third injection, the corticosteroid group reported a statistically significant greater improvement in pain via Visual Analog Scale (VAS); however at 6-month follow-up, the prolotherapy group reported a statistically significant greater improvement in pain. At the 6-month follow-up, both the prolotherapy and corticosteroid groups reported improved overall hand function; however again, the prolotherapy group had a significant larger effect at this time point, overall suggesting better long-term effects of prolotherapy as compared with the expected, short-lived effects of intra-articular steroid.

In 2018, Rahimzadeh et al. compared intra-articular knee prolotherapy injections with platelet-rich plasma (PRP) injections [29]. Forty-two patients with stage 1 or 2 Kellgren-Lawrence knee OA were randomized into a PRP group (7 cc PRP solution) versus prolotherapy group (7 cc 25% dextrose solution). Participants received these injections twice, 1 month apart. All participants saw a rapid decrease in overall WOMAC score at both 1 month and 2 months following the first injection. WOMAC score then rose at the 6-month mark, but was still statistically significantly lower than baseline score. There was no statistically significant difference in these scores between the two groups, suggesting a possible comparable efficacy and underlying mechanism to both PRP and prolotherapy; however, of note was the substantially lower cost associated with performing the dextrose injections.

## *Intra-articular Versus Extra-articular Injections for Joint Pain*

Because of the wide variation of practice and different indications of use, it has been questioned whether it is the intra-articular injection itself that results in improvements in OA symptoms or the peri-articular injection effects. Farpour performed

a randomized controlled trial of 52 adults with primary knee OA (grade 2–3 Kellgren-Lawrence) for at least 3 months. Participants were randomized to either an intra-articular injection group or a peri-articular injection group. Injections were performed twice within a 2-week interval. In the peri-articular group, up to three points of tenderness surrounding the knee were identified and injected with a total of 6 cc of 25% dextrose. In the intra-articular group, 6 cc total of 25% dextrose was injected intra-articularly. Ultimately, following injections, both groups reported comparable improvements in pain and function via Visual Analog Scale, Oxford Knee Scale, and WOMAC over 4–8 weeks post-injection, without any superiority between the two methods [30].

Rezasoltani et al. did the same: in a randomized, double-blinded controlled trial, 104 patients with chronic knee OA were randomized to an intra-articular versus peri-articular injection group. In the intra-articular group, 8 cc of 10% dextrose and 2% lidocaine was injected into the knee joint. In the peri-articular group, 5 cc of 20% dextrose and 5 cc of 1% lidocaine was injected subcutaneously at 4 points in the periarticular knee. Injections were repeated at 1 and 2 weeks after the first injection. In this study, VAS was significantly lower in the peri-articular group as compared with the intra-articular group at 2-, 3-, 4-, and 5-month follow-up (but not at 1 month). Walking and stair climbing difficulty, morning stiffness, and joint locking improved in both groups and were not statistically significant between groups [ 31].

There has not been much investigation into efficacy of intra-articular dextrose injections past a 1-year follow-up period, and long-term outcomes are largely lacking. Only one study by Rabago et al. examined long-term outcomes in patients who had received intra-articular knee dextrose injections at 2.5 years of follow-up. Sixty-five patients who received up to 5 intra-articular injections over 17 weeks were observed to experience clinically meaningful improvements in WOMAC scores at 1 year of follow-up; these same patients reported continued improvement in WOMAC score at 2.5 years of follow-up, with an average of about 36% of improvement in WOMAC score at 2.5 years as compared with baseline. No adverse effects were observed [32].

## *Sacroiliac Joint and Axial Spine Prolotherapy Treatments*

Very little is known about the effect of prolotherapy injections on pain within axial joints; however, several small studies exist. Kim et al. performed a prospective, randomized controlled trial comparing dextrose prolotherapy versus corticosteroid to the sacroiliac joint to address low back pain attributed primarily to SI joint dysfunction [33]. Forty-eight patients with SI joint pain (confirmed by 50% or greater improvement in response to local anesthetic block) lasting 3 months or longer were randomized to receive either intra-articular 25% dextrose or triamcinolone injections to the SI joint, performed under fluoroscopic guidance. Pain and disability scores were assessed at baseline, 2 weeks, and monthly following this injection. All scores

were significantly improved from baseline in both groups at 2 weeks post-injection; however, at 15 months, the prolotherapy group had a cumulative incidence of 50% or greater improvement in symptoms of 58.7% versus 10.2% in the steroid group; this difference was found to be statistically significant. Additionally, Cusi et al. performed a prospective descriptive study of 25 patients who also received SI joint injections with dextrose and demonstrated subsequent improvements in back pain disability ratings; however, the targeted structure was not the joint space itself, but rather the dorsal interosseous ligament of the affected SI joint [34]. Finally, Hooper et al. described a retrospective case series of patients with "chronic spinal pain" treated with dextrose prolotherapy [35]. One hundred and seventy-seven patients with multi-site chronic axial back pain were treated with 20% dextrose injections to the facet capsules of the cervical, thoracic, and/or lumbar spine. Additionally, iliolumbar and dorsal sacroiliac ligaments were injected in patients with a chief complaint of lower back pain. Ninety-one percent of patients reported reductions in pain; 85% reported improvements in ADLs, and 84% reported improvements in ability to work over 2.5 years of follow-up. These patients were not compared against patients who received medical management, physical therapy, or other axial spine injections.

Given the widespread prevalence of osteoarthritis and the cost burden it imparts, dextrose injections represent an inexpensive and accessible potential tool for symptom management. However, current quality and level of evidence leaves much to be desired. There are many pitfalls associated with the research examining efficacy of prolotherapy as a viable clinical tool for osteoarthritis management. For one, there is a wide degree of heterogeneity among studies, especially with regard to sample size, blinding, controls, composition of injectate, and injection protocols. Percent of dextrose injected ranged from 10% to 25%. Injection volumes were highly variable. The number of injections performed and anatomical locations of the injections were variable. Some studies performed injections blindly, while others used ultrasound guidance for needle localization to ensure accuracy. Some injections involved additional use of anesthetic agents such as lidocaine, which have known chondrotoxic effects, potentially muddying outcomes. The vast majority of studies were performed on the knee, with overall lack of representation of other commonly affected joints in OA, such as the hip and shoulder.

Despite these limitations, existing research provides some promising insights. For example, comparable effects between dextrose and PRP injections may highlight prolotherapy as a cost-effective alternative to more expensive and time-consuming regenerative therapies. The efficacy of extra-articular injections suggests an important role of dynamic and soft tissue stabilizers as pain generators in OA. Improvements in pain observed in conjunction with increased chondral volume lend exciting evidence to the theoretical "proliferative" nature of prolotherapy, and the capacity of intra-articular injections to stimulate chondrogenesis in general. Further research is needed to corroborate these potential tissue changes, to identify ideal injectate volumes and compositions, and to identify utility and feasibility in other commonly affected joints.

## Tendinopathy Clinical Studies

The most data, in terms of quantity and quality, evaluating the use of prolotherapy versus control injections exist for tendinopathies. In particular, the evidence is most robust for chronic, painful, overuse tendinopathies [36, 37]. Overuse tendinopathies secondary to repetitive motion share similar micro- and macroscopic features, suggesting shared pathologic processes. For example, tendinopathies of the common extensor tendon (lateral epicondylitis), Achilles tendon, and patellar tendon share similar histological and sonographic features, suggesting a common, noninflammatory pathophysiology [38]. Studies of prolotherapy in these cases is reviewed here.

### *Lateral Epicondylitis*

Lateral epicondylitis (LE) is a degenerative disease caused by repetitive microtrauma that leads to angiogenesis and fibroblast proliferation [39]. There has been a hypothesis that interrupting the increased blood vessel infiltration and fibroblast proliferation may improve pain in epicondylitis. However, a study investigating purely blood vessel sclerosis did not demonstrate significant improvement. Thirty-six participants with lateral epicondylitis did not demonstrate a significant improvement after an ultrasound-guided lauromacrogol injection (lauromacrogol, or polidocanol, is not a typical prolotherapy injectate; it is a blood vessel sclerosing agent) [40].

Effects of prolotherapy have been studied for lateral epicondylitis with varied results. A double-blinded, randomized controlled study with 24 participants compared to placebo (normal saline) was conducted with three injections of hypertonic glucose, sodium morrhuate, and local anesthetic over 8 weeks. The average duration of epicondylalgia among the participants was 1.9 years. There was no significant difference in symptom improvement noted in the short term (immediately prior to the third injection), but there was a difference in the intermediate term. Of note, in this pilot study, all ten participants receiving prolotherapy reported pain at the injection site, as did all ten of the participants receiving placebo injections [41].

Another randomized controlled trial compared prolotherapy with local corticosteroid injection for LE. Seventeen participants were given two injections, 1 month apart, of either phenol-glycerine-glucose, dextrose, and sodium morrhuate or methylprednisolone. There were no clinically significant differences between groups. However, the prolotherapy group showed improvements from baseline in the Visual Analog Scale (VAS) and the Disabilities of the Arm, Shoulder, and Hand (DASH) at both 3-month and 6-month time points. The methylprednisolone group only showed improvements in the DASH at the 3-month but not 6-month time points [42].

Another randomized trial by Rabago et al. randomized patients into three groups: injections of 50% dextrose at 1, 4, and 8 weeks; 50% dextrose with 5% sodium morrhuate at 1, 4, and 8 weeks; and no intervention. The primary outcome was the Patient-Reported Tennis Elbow Evaluation score. Both experimental groups showed

statistically significant improvements in the primary outcome at multiple time points in the 32-week follow-up period [43]. However, the study is limited by the lack of a control injection. Furthermore, other outcome measures in this study, including grip strength and magnetic resonance imaging severity, were mostly unchanged.

## *Achilles Tendinopathy*

In 20 patients with Achilles tendinopathy, an ultrasound-guided lauromacrogol injection did not demonstrate a significant improvement in symptoms, though there was a suggestive trend, ($p = 0.07$) [8]. Another study of 43 participants compared prolotherapy alone, eccentric exercise alone, and a combination of the two [44]. There were no differences in the outcomes across the three groups in either the short, intermediate, or long term. However, the prolotherapy group was the quickest to achieve favorable outcomes.

In another study of 36 participants with conservative treatment refractory Achilles tendinopathy, ultrasound-guided injections of dextrose and anesthetic at 6-week intervals improved pain scores and neovascularity measured by ultrasound in 55% of the participants [45]. It is crucial to note that this study has no control group.

## *Rotator Cuff Tendinopathy*

There have been several studies in recent literature investigating the effects of prolotherapy treatment for chronic rotator cuff tendinopathy. Rotator cuff tendinopathy is one of the most common causes of chronic shoulder pain in the absence of active inflammation. It is typically treated with exercise and physical therapy. Those that are refractory to conservative management can be difficult to treat with many techniques attempted by clinicians including corticosteroid injections, PRP injections, and prolotherapy. Results of prolotherapy treatment for rotator cuff tendinopathy have shown favorable results for pain control, particularly when compared to physiotherapy alone. But there are mixed results when compared to other injection therapies. Studies have demonstrated improvement in supraspinatus tendon structure with prolotherapy injections, but not significantly different from improvements seen with other treatments.

Comparing prolotherapy to traditional physiotherapy treatment, a few authors have found favorable outcomes for prolotherapy treatment. Lee et al. performed a retrospective case-control study of patients with nontraumatic refractory rotator cuff disease ($n = 151$) who were unresponsive to 3 months of physical therapy. The treatment group received 16.5% dextrose 10 mL solution ($n = 63$) while the control group continued with physical therapy ($n = 63$). The average number of prolotherapy injections in the treatment group were 4.8 +/− 1.3. There was significant improvement in the prolotherapy treatment group in VAS, Shoulder Pain and

Disability Index (SPADI), isometric strength of shoulder abduction, and shoulder AROM at over 1-year follow-up [46].

Seven et al. conducted a randomized controlled study ($n$ = 120) of patients with chronic rotator cuff lesions for greater than 6 months. Controls treated with physical therapy 3 times a week were compared to a prolotherapy treatment group. All conducted home exercise programs. Of the 101 patients included in the study (44 in the control group, 57 in the prolotherapy group), both groups achieved significant improvements in VAS, SPADI, Western Ontario Rotator Cuff (WORC) index, and shoulder ROM ($p < 0.001$). Intergroup comparisons demonstrated significant differences in VAS, SPADI, WORC index, shoulder abduction, shoulder flexion, and shoulder internal rotation at over 1 year follow-up favoring prolotherapy treatment. Prolotherapy treatment resulted in 92.9% of patients reporting excellent or good outcomes compared to the control group with 56.8% reporting excellent or good outcomes [47].

A smaller randomized controlled prospective study by George et al. included 12 patients with focal supraspinatus tendinosis after 1 month of PT. Seven patients received 0.5–1 mL prolotherapy injection (12.5% dextrose, 0.5% lidocaine) and was compared to 5 patients who continued with standard physical therapy without interventions. He found superior and significant improvement in shoulder abduction ($p = 0.03$) and sleep score ($p = 0.027$) in the prolotherapy group. Echogenicity on ultrasound also significantly increased at the end of treatment for the prolotherapy group ($p = 0.009$). However, no significant reduction in pain score was seen in the injection group (43.5%) compared to the control group (25%) at 12 weeks ($p > 0.005$) [48].

A few authors studied prolotherapy compared to normal saline injections. Lin et al. demonstrated short-term pain relief in chronic rotator cuff tendinopathy. He conducted a double-blinded placebo-controlled trial ($n$ = 31) with the treatment group receiving ultrasound-guided injection of dextrose 20% compared to a control group that received ultrasound-guided injection of normal saline 5% to the tendinopathic supraspinatus tendon. Outcome measures included VAS, SPADI, shoulder AROM, ultrasound thickness, and histogram and were measured at baseline, 2 weeks, and 6 weeks after intervention. He found that the prolotherapy group demonstrated significant improvement in VAS ($P = 0.001$), SPADI score ($P = 0.017$), shoulder AROM ($P = 0.039$), and shoulder abduction ($P = 0.043$) at 2 weeks after injection. However, the effects were not sustained at 6 weeks. No differences in ultrasound morphological changes were seen in the participants in either group [49].

Another randomized double-blinded control trial that studied the effects of prolotherapy compared to saline injections was conducted by Bertrand et al. His team studied patients with chronic moderate to severe shoulder pain due to rotator cuff tendinopathy for 7.6+/−9.6 years with ultrasound confirmation of supraspinatus tendinosis/tear ($n$ = 73). Patients were stratified in to three groups, each receiving three monthly injections of dextrose into the supraspinatus enthesis, saline into the supraspinatus enthesis, and saline above the enthesis. The primary outcome was the VAS and the secondary outcome was the ultrasound shoulder pathology rating scale (USPRS). At 9-month follow-up, 59% of dextrose enthesis injection patients maintained improvement in pain, with VAS score demonstrating >2.8 improvement, compared to saline enthesis injection patients, 37% ($p$ = 0.088), and superficial

saline injection patients, 27% ($p = 0.017$). Dextrose enthesis satisfaction scores were 6.7 compared to saline, 4.7, and superficial saline, 3.9. USPRS demonstrated no difference between groups ($P = 0.734$). Overall, dextrose resulted in superior long-term pain improvement and satisfaction compared to blinded saline injections. All showed some improvement, but no significant differences between groups on improvement of tendinopathy were seen on ultrasound [50].

Comparing prolotherapy injections to subacromial bursa corticosteroid injections, Cole et al. performed a prospective randomized double-blinded clinical trial. His group compared prolotherapy injection into tendinopathic supraspinatus tendons ($n = 17$) to corticosteroid bursa injections ($n = 19$). There was significant reduction of pain with overhead activities at 3 months in only the prolotherapy group. By 6 months, both groups demonstrated significant reduction of pain without any difference between groups ($p = 1.0$). Both the prolotherapy and corticosteroid groups demonstrated significant improvement of the supraspinatus tendon on ultrasound compared to baseline at 3 months, but no significant difference between groups ($p = 0.44$) [51].

Finally, Lin et al. conducted a meta-analysis systematic review of randomized controlled trials comparing corticosteroid, nonsteroidal anti-inflammatory drugs (NSAIDs), hyaluronic acid, botulinum toxin, PRP, and prolotherapy in patients with RTC tendinopathy. Out of 18 studies that were included, his team found that corticosteroid was more effective only in the short term in both pain reduction and functional improvement. Prolotherapy significantly reduced pain compared with placebo in the long term (over 24 wks; SMD, 2.63; 94% CI, 1.88–3.38). PRP significantly improved shoulder function compared to placebo in the long term (24 wks; SMD, 0.44; 95% CI, 0.05–0.84) [52].

## Side Effects and Adverse Events

Most adverse events associated with prolotherapy injections are related to the treatment location. In a study by Yelland et al., prolotherapy used to treat generic low back pain caused immediate pain in the low back in 88% of participants. Few patients also suffered from headaches after treatment which resolved within 1 week. Few patients suffered from leg pain with neurological features [53]. Several other studies reported similar events, most commonly, pain and stiffness at the injection site anywhere from 12 to 96 hours after the injections [54–57]. Rare adverse events in these studies include sleep disturbance due to "psychological trauma," irregular menses, lumbar puncture headache, and radicular pain. Rarer still, serious adverse events in patients receiving prolotherapy for low back pain include two cases of meningitis (both resolved with treatment) [58], adhesive arachnoiditis (requiring ventriculostomy and craniotomy ultimately resulting in post-operative death, a case report published in the Journal of the American Medical Association) [59], and encephalomyelitis (treated with ventriculojugular shunt resulting in steady improvement) [60].

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