# Prolotherapy: A Clinical Review of Its Role in Treating Chronic Musculoskeletal Pain

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**Abstract:** Prolotherapy is a technique that involves the injection of an irritant, usually a hyperosmolar dextrose solution, typically in the treatment of chronic painful musculoskeletal conditions. Despite its long history and widespread use as a form of complementary therapy, there still are disparities over its optimal indications and injection preparations. There are, however, numerous studies available regarding the use and efficacy of prolotherapy for various musculoskeletal conditions. The most frequently published indication is in the treatment of chronic low back pain, but there are recent studies that examined its use in the management of refractory tendinopathies as well as osteoarthritis. There is growing 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. There is also evidence to suggest that prolotherapy is effective in treating refractory tendinopathies, particularly for lateral epicondylosis and Achilles tendinopathy. Additional larger, randomized controlled trials are needed to make specific recommendations regarding ideal protocols and indications. There is emerging evidence for the use of prolotherapy as a treatment option for osteoarthritis; however, further studies are needed to conclusively demonstrate its efficacy. Overall, prolotherapy remains a promising option for the treatment of painful musculoskeletal conditions, particularly when other standard treatments have proved ineffective.

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## INTRODUCTION

In an aging and working society, the development of degenerative diseases and overuse injuries is common and may lead to chronic conditions, including low back pain (LBP) and various tendinopathies. Given the significant prevalence of chronic musculoskeletal pain and the impact that it has on economic productivity and quality of life, there is much interest in finding ways to prevent and successfully treat both overuse and degenerative musculoskeletal conditions.

The use of various injection therapies by medical practitioners for the treatment of musculoskeletal conditions is widespread. The material most commonly injected into joints and peritendinous areas is often a combination of corticosteroid and anesthetic. However, there are several other agents and techniques that are currently being used, including prolotherapy, platelet-rich plasma, autologous whole blood, dry needling, and acupuncture. The aim of this clinical review is to summarize the current literature that is available on the efficacy of prolotherapy as a therapeutic option for various musculoskeletal conditions.

The use of injections in the management of painful musculoskeletal conditions is widespread among practitioners who treat patients with tendinous or joint complaints. Corticosteroid and anesthetic preparations are almost always the initial injection therapy of choice, and there is an abundance of literature that examines the efficacy of this approach for various conditions. Given the prevalence of chronic painful musculoskeletal conditions and refractory nature that some patients experience, alternative injectants have been of interest to medical providers and researchers for years. The basic science of the pathophysiology of

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**Table 1.** *Solutions commonly used in prolotherapy and their proposed mechanisms of action*

| Injected Solution | Mechanism of Action |
|---|---|
| Hyperosmolar dextrose | Creates hypertonic atmosphere, which leads to cell rupture (3)<br>Upregulates expression of platelet-derived growth factors (3) |
| Morrhuate sodium | Attracts inflammatory mediators (1)<br>Vascular sclerosant (3,5) |
| Phenol-glycerine-glucose | Cellular irritant (1) |

tendinopathy is becoming better understood, which has resulted in the development and investigation of other injectants.

## DEFINITION OF PROLOTHERAPY

Prolotherapy refers to the injection of an irritant into a joint space, ligament, or tendon insertion site as a complementary medical treatment, with the main goal being pain relief. Although many different solutions have been used throughout the past 100 years that prolotherapy has been in practice [1], the most commonly reported and studied agents are hyperosmolar dextrose, phenol-glycerine-glucose, and morrhuate sodium [2,3]. Phenol-glycerine-glucose is no longer used, but it was included in the majority of the earlier published studies. Hyperosmolar dextrose appears to be the most commonly used agent today, with morrhuate sodium used slightly less often [4].

## MECHANISM OF ACTION

Mechanisms of action that lead to improvement in symptoms are incompletely understood. Current hypotheses suggest that the presence of a local irritant may attract inflammatory mediators and possibly stimulate the release of growth factors [1] or by acting as a vascular sclerosant [5] (Table 1).

Jensen et al investigated the histochemical [6,7] and biomechanical [4] responses to prolotherapy by comparing dextrose, morrhuate sodium, and phenol-glycerine-glucose in medial collateral ligaments (MCL) in rats. They showed that tissue inflammation increased after prolotherapy compared with no injection, although the inflammatory response was variable among injectants and location of injection, and not uniformly different compared with dry needling or saline solutions [5]. The inflammatory markers were largely absent by 72 hours after injection. The theory that the induced inflammatory response might lead to decreased ligamentous laxity was not supported by the study by Jensen et al [4], which demonstrated an increase in a MCL cross-sectional area but no other change in mechanical properties (strength and stiffness) or laxity after injection with dextrose solution.

## EVIDENCE REVIEW OF PROLOTHERAPY IN PRACTICE

### Chronic LBP

Prolotherapy has been used in practice for approximately 100 years, and there are numerous studies available on its applications and efficacy. However, the majority of the initial studies were pilot-level clinical trials. In recent years, there has been an increase in the number of randomized controlled trials (RCT) and prospective studies. However, it can still be a challenge to draw conclusions because of the wide variety of injection techniques and indications included.

A systematic review on prolotherapy for all conditions by Rabago et al [1,8] yielded 42 studies published since 1937, which consisted mostly of case reports and case series. In general, these studies were not randomized, lacked control groups, and included the use of multiple types of injectants and techniques. The most commonly encountered indication studied was for nonspecific LBP but also included sacroiliac dysfunction, osteoarthritis, acromioclavicular separations, shoulder pain, cervical injuries, and fibromyalgia. The researchers acknowledged the methodologic limitations in all of the included studies and recognized that many of the older publications used injected solutions no longer in practice. Despite this, positive results were reported in randomized and nonrandomized trials, and established a foundation for future research.

In recent years, there have been RCTs that evaluated the effectiveness of prolotherapy in the treatment of nonspecific and specific causes of LBP. Four RCTs [9-12] have been identified that investigated prolotherapy in the treatment of nonspecific LBP, and 4 studies [13-16] that examined LBP specifically because of sacroiliac joint dysfunction, refractory coccygodynia, and severe degenerative disk disease that caused radiculopathy. Of the 4 RCTs that examined prolotherapy in nonspecific LBP, 2 reported positive outcomes [9,11] and 2 reported outcomes that did not reach statistical significance [10,12]. The 2 studies with positive findings used protocols that involved adjunctive therapies, including injection of corticosteroids, spinal manipulation, and exercise, which make it impossible to isolate the contribution of the prolotherapy to the improvement in symptoms. The other 2 studies did not report any adverse outcomes and showed trends toward improved pain and disability scores; however, the difference between the prolotherapy groups and controls were not statistically significant.

A Cochrane review [17] published in 2007 concluded that there was "conflicting evidence regarding the efficacy of prolotherapy injections for patients with chronic LBP." The researchers found that prolotherapy is not effective when used alone in treating LBP but may improve symptoms and disability when combined with other modalities or interventions. A study by Cusi et al [13] involved the use of computed tomography-guided injections of hyperosmolar dextrose into

a painful, dysfunctional sacroiliac joint in 25 patients. They reported significant improvement in pain and disability scores from the patients' baseline scores; however, there were no control subjects used in this study. A similar study by Kim et al [14] compared the effects of hyperosmolar dextrose versus triamcinolone acetonide fluoroscopically guided intra-articular injections into painful sacroiliac joints. Their results showed improvements in pain and disability scores from baseline in both groups;however, the effects of the dextrose group lasted longer than the steroid group.

Khan et al [15] studied 37 patients with chronic coccygodynia. The patients received up to 3 dextrose-lidocaine injections into the coccyx and had improved visual analog scores in 30 of the 37 patients, and no improvement in the remaining 7 patients. Miller et al [16] studied the effects of hypertonic dextrose-bupivacaine intradiskal injections on patients with chronic advanced diskogenic leg pain, with or without back pain. The researchers reported that 43.4% of patients experienced >18 months of improvement in pain. These studies offer promise for prolotherapy for a host of low back conditions and support the need for further RCTs aimed at more precise indications when treating LBP with this approach.

## Chronic Tendinopathies

Despite the abundant but inconsistent evidence for the use of prolotherapy in the treatment of specific and nonspecific chronic LBP, there is more promising recent evidence for its use in treating painful tendinopathies. Tendinopathy refers to a painful clinical condition that occurs around a tendon, often as a result of overuse. This condition is often referred to as "tendinitis," however, scientific studies have proved a general absence of inflammatory cells and the development of a structurally pathologic tendon from degenerative processes and neovascularization [17]. Although it has not been proven that prolotherapy leads to a sustained inflammatory response [3], it does appear that tendons and ligaments have increased strength and size after injection with morrhuate sodium [3]. Prolotherapy has been used clinically for multiple tendinopathies and has been studied for the treatment of lateral epicondylosis, Achilles tendinopathy, plantar fasciitis, and hip adductor tendionpathies.

In a pilot study published in 2008, Scarpone et al [18] randomized 20 adults with refractory lateral epicondylosis to receive either normal saline solution versus dextrose and morrhuate sodium injections at 0-, 4-, and 8-week intervals. The dextrose-morrhuate sodium group reported statistically significant improvements in pain scores and grip strength that persisted at 52 weeks. This is one of the few studies that demonstrate efficacy for prolotherapy up to 1 year after treatment and is the only level 1 RCT that studied prolotherpay for treatment of tendinopathies.

Maxwell et al [19], with the use of ultrasound guidance, performed intratendinous injections in 36 adults with chronic, refractory Achilles tendinopathy by using a dextrose and anesthetic solution at 6-week intervals. The researchers reported statistically significant reductions in pain scores at 6 weeks as well as decreased neovascularity as measured by ultrasound in 55% of the tendons. There was no significant change in the hypoechoic areas, which are postulated to represent collagen degeneration, in 82% of the tendons. It should be noted that this study excluded patients without improvement in their data analysis and did not have any control subjects. Another study, by Yelland et al [20], showed that prolotherapy in combination with eccentric loading exercises compared with either treatment alone, provided the most relief in the first 6 weeks in the management of Achilles tendinopathy but yielded no significant difference between the treatment groups at 12 months.

A case series that examined the efficacy of prolotherapy on hip adductor tendinopathy in male athletes engaged in kicking sports was published by Topol et al [21]. Subjects with groin pain for a mean of 15.5 months that was unresponsive to specified physical therapy were injected monthly with dextrose and lidocaine into the areas of maximal tenderness. The average number of injections was 2.8. Twenty of 24 athletes had complete resolution of painful symptoms, and nearly all the participants were able to return to their sport without restrictions as measured by pain and functional scales.

A pilot study by Ryan et al [22] examined the effects of prolotherapy on patients with chronic plantar fasciopathy who had failed conservative treatments. The researchers injected 36 symptomatic adults with hyperosmolar dextrose and lidocaine solution under ultrasound guidance. They then used visual analog scales for pain at rest, during activities of daily living, and during or after physical activity, and reported significantly decreased mean scores in all areas at the final treatment consultation.

## Osteoarthritis

There is some evidence that demonstrates the efficacy of prolotherapy in the treatment of osteoarthritis. Reeves et al looked at the treatment of knee [23] and finger and/or thumb osteoarthritis [24]. Both studies included patients with at least 6 months of knee or finger pain and radiographic evidence of significant joint space narrowing, a moderate-sized osteophyte, or both in at least one compartment of the affected joint space. Participants in both studies were randomized to receive either dextrose and lidocaine, or lidocaine and bacteriostatic water injections, at 0, 2, and 4 months. Both studies showed positive outcomes, with improvement in pain at rest and with activity, joint stability, and range of motion compared with control groups. However, neither study's results achieved statistical significance.

## DISCUSSION AND CLINICAL RECOMMENDATIONS

As the evidence reviewed above outlines, the current most promising indication for the use of prolotherapy appears to be in the treatment of tendinopathies. As a procedure, it is relatively safe, with few adverse effects or contraindications [1]. Absolute contraindications are similar to any other type of injection and include the presence of an overlying cellulitis or septic joint. Adverse effects include mild pain or bleeding at the injection site or the development of a postinjection flare, similar to corticosteroid injections. These usually are self-limited and often resolve within 1 or 2 days. Historically, there have been a handful of serious adverse events, such as neurologic impairment during perispinal injections with highly concentrated solutions, and one reported death with the use of zinc sulfate, however, these were related to the use of injectants that are no longer used in practice [1]. Pneumothoraces, spinal headaches, and nerve damage also have been reported as a result of neck and spine prolotherapy injections but at the same rate as other spinal injection procedures [1].

There is growing evidence to recommend the use of prolotherapy in the treatment of refractory tendinopathies, specifically lateral epicondylitis and Achilles tendinopathy. Given the similar pathologic findings of tendinopathies in different anatomic locations, the researchers believe that it is reasonable to try prolotherapy for other, less studied tendinopathies when first-line treatments fail. There is inadequate evidence to recommend the use of prolotherapy as a sole treatment for LBP but may be used in conjunction with other therapies. Early studies indicate promising results in the treatment of osteoarthritis, but further clinical trials are needed before a sound recommendation can be made.

## REFERENCES


1. Rabago D, Slattengren A, Zgierska A. Prolotherapy in primary care practice. Prim Care 2010;37:65-80.
2. Dagenais S, Ogunseitan O, Halderman S, et al. Side effects and adverse events related to intraligamentous injection of sclerosing solutions (prolotherapy) for back and neck pain: a survey of practitioners. Arch Phys Med Rehabil 2006;87:909-913.
3. Rabago D, Best TM, Zgierska AE, Zeisig E, Ryan M, Crane D. A systematic review of four injection therapies for lateral epicondylosis: prolotherapy, polidocanol, whole blood and platelet-rich plasma. Br J Sports Med 2009;43:471-481.
4. Jensen K, Rabago D, Best TM, Patterson JJ, Vanderby R. Response of knee ligaments to prolotherapy in a rat injury model. Am J Sports Med 2008;36:1347-1357.
5. Alfredson H, Ohberg L. Neovascularisation in chronic painful patellar tendinosis: promising results after sclerosing neovessels outside the tendon challenge the need for surgery. Knee Surg Sports Traumatol Arthrosc 2005;13:74-80.
6. Jensen K, Rabago D, Best TM, et al. Early inflammatory response of knee ligaments to prolotherapy in a rat model. J Orthop Res 2008;26:816-823.
7. Jensen KT. Healing response of knee ligaments to prolotherapy in a rat model [PhD dissertation]. Madison, WI: University of Wisconsin; 2006.
8. Rabago D, Best TM, Beamsley M, et al. A systematic review of prolotherapy for chronic musculoskeletal pain. Clin J Sport Med 2005;15:376-380.
9. Klein RG, Eek BC, DeLong WB, et al. A randomized double-blind trial of dextrose-glycerine-phenol injections for chronic, low back pain. J Spinal Disord 1993;6:23-33.
10. Dechow E, Davies RK, Carr AJ, et al. A randomized, double-blind, placebo-controlled trial of sclerosing injections in patients with chronic low back pain. Rheumatology 1999;38:1255-1259.
11. Ongley MJ, Klein RG, Dorman TA, et al. A new approach to the treatment of chronic low back pain. Lancet 1987;ll:143-146.
12. Yelland M, Glasziou P, Bogduk N, et al. Prolotherapy injections, saline injections, and exercises for chronic low back pain: a randomized trial. Spine 2004;29:9-16.
13. Cusi M, Saunders J, Hungerford B, et al. The use of prolotherapy in the sacro-iliac joint. Br J Sports Med 2010;44:100-104.
14. Kim WM, Lee HG, Jeong CW, Kim CM, Yoon MH. A randomized controlled trial of intra-articular prolotherapy versus steroid injection for sacroiliac joint pain. J Altern Complement Med 2010;16:1285-1290.
15. Khan SA, Kumar A, Varshney MK, et al. Dextrose prolotherapy for recalcitrant coccygodynia. J Orthop Surg 2008;16:27-29.
16. Miller MR, Mathews RS, Reeves KD. Treatment of painful advanced internal lumbar disc derangement with intradiscal injection of hypertonic dextrose. Pain Physician 2006;9:115-121.
17. Dagenais S, Yelland MJ, Del Mar C, Schoene ML. Prolotherapy injections for chronic low-back pain. Cochrane Database Syst Rev 2007;(2):CD004059.
18. Scarpone M, Rabago D, Zgierska A, et al. The efficacy of prolotherapy for lateral epicondylitis: a pilot study. Clin J Sport Med 2008;18:248-254.
19. Maxwell NJ, Ryan MB, Taunton JE, et al. Sonographically guided intratendinous injection of hyperosmolar dextrose to treat chronic tendinosis of the Achilles tendon: a pilot study. AJR Am J Roentgenol 2007;189:W215-W220.
20. Yelland MJ, Sweeting KR, Lyftogt JA, Ng SK, Scuffham PA, Evans KA. Prolotherapy injections and eccentric loading exercises for painful Achilles tendinosis: a randomised trial. Br J Sports Med 2011;45:421-428.
21. Topol GA, Reeves KD, Hassanein KM. Efficacy of dextrose prolotherapy in elite male kicking-sport athletes with groin pain. Arch Phys Med Rehabil 2005;86:697-702.
22. Ryan MB, Wong AD, Gillies JH, et al. Sonographically guided intratendinous injections of hyperosmolar dextrose/lidocaine: a pilot study for the treatment of chronic plantar fasciitis. Br J Sports Med 2009;43:303-306.
23. Reeves KD, Hassanein K. Randomized prospective double-blind placebo-controlled study of dextrose prolotherapy for knee osteoarthritis with or without ACL laxity. Altern Ther Health Med 2000;6:68-80.
24. Reeves KD, Hassanein K. Randomized, prospective, placebo-controlled double-blind study of dextrose prolotherapy for osteoarthritic thumb and finger (DIP, PIP, and trapeziometacarpal) joints: evidence of clinical efficacy. J Altern Complement Med 2000;6:311-320.