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Evidence-informed management of chronic low back pain with prolotherapy

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Abstract **EDITORS' PREFACE:** The management of chronic low back pain (CLBP) has proven to be very challenging in North America, as evidenced by its mounting socioeconomic burden. Choosing among available nonsurgical therapies can be overwhelming for many stakeholders, including patients, health providers, policy makers, and third-party payers. Although all parties share a common goal and wish to use limited health-care resources to support interventions most likely to result in clinically meaningful improvements, there is often uncertainty about the most appropriate intervention for a particular patient. To help understand and evaluate the various commonly used nonsurgical approaches to CLBP, the North American Spine Society has sponsored this special focus issue of *The Spine Journal*, titled Evidence-Informed Management of Chronic Low Back Pain Without Surgery. Articles in this special focus issue were contributed by leading spine practitioners and researchers, who were invited to summarize the best available evidence for a particular intervention and encouraged to make this information accessible to nonexperts. Each of the articles contains five sections (description, theory, evidence of efficacy, harms, and summary) with common subheadings to facilitate comparison across the 24 different interventions profiled in this special focus issue, blending narrative and systematic review methodology as deemed appropriate by the authors. It is hoped that articles in this special focus issue will be informative and aid in decision making for the many stakeholders evaluating nonsurgical interventions for CLBP.

Keywords: Chronic low back pain; Prolotherapy; Intraligamentous injection

Description

Terminology

Intraligamentous injection of solutions aimed at promoting connective tissue repair is commonly known as prolotherapy, which has been defined as ''the rehabilitation of an incompetent structure (such as a ligament or tendon) by the induced proliferation of new cells'' [1]. Common synonyms for this therapy include regenerative injection therapy, growth factor stimulation injection, nonsurgical tendon, ligament and joint reconstruction, proliferant injection, prolo,

FDA device/drug status: investigational or not approved for this indication (Proliferol).

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and joint sclerotherapy [2]. Proponents of this intervention generally dislike the term sclerotherapy—which is associated with the formation of unorganized scar tissue—rather than the more beneficial, organized connective tissue that prolotherapy is intended to generate [3,4].

History

Prolotherapy has been used to treat chronic low back pain (CLBP) for over 60 years [5] and was originally adapted from sclerotherapy, which involves injection of irritant solutions to induce acute inflammation, stimulate connective tissue growth, and promote formation of collagen tissue [6]. Sclerotherapy was commonly used to close the lumen in varicose veins, and in nonsurgical abdominal hernia repair [7]. Based on the hypotheses that joint hypermobility could be attributed to incomplete connective tissue repair after an injury, this treatment approach was later applied to chronic musculoskeletal conditions suspected of being related to ligament or connective tissue laxity. The use of prolotherapy for CLBP was promoted in the 1950s by a general surgeon named George S. Hackett, who published large case series claiming very high rates of success for a condition that had few valuable surgical options at that time.

Frequency of use

A survey of 908 primary care patients receiving opioids for chronic pain—most commonly CLBP (38.4%)—reported that 8.3% had used prolotherapy in their lifetime, and 5.9% had used it in the past year; those who reported using prolotherapy did do an average of 3.5 times in the past year [8].

Subtypes

Although there are no formal subtypes of prolotherapy, there is substantial heterogeneity in the treatment protocols used by different practitioners. The approaches to prolotherapy generally differ according to the type of solution injected, the volume and frequency of injections, and use of cointerventions.

The method used in studies by Ongley et al. [9,10] typically involves six weekly injections of 20 to 30 ml of a solution containing dextrose 12.5%, glycerin 12.5%, phenol 1%, and lidocaine 0.25% into multiple preselected lumbosacral ligaments. Injections are usually accompanied by spinal manipulation and instructions for the patient to perform repeated standing lumbar flexion-extension exercises for several weeks. This approach may also use corticosteroid injections into tender lumbosacral areas before the first session of prolotherapy.

Prolotherapy methods used in other studies involved a greater number of injections [6–10] at longer intervals (biweekly-monthly) with a smaller gauge needle, a lower injected volume (10–20 ml), and a solution containing only dextrose 10% to 20% and lidocaine 0.2% to 0.5% [11]. The rationale provided by proponents of this latter method is that it minimizes the inflammatory reaction and is therefore more easily tolerated by patients.

It should be noted that these methods of prolotherapy were developed clinically based largely on anecdotal evidence and practitioner preference, many of whom eventually modify these methods further and tailor treatments to individual patient needs.

General description

The treatment procedure for prolotherapy varies a great deal among practitioners. The treatment begins with the patient gowned and lying prone on a treatment table. Through manual palpation, the physician first identifies—and possibly marks with a pen—landmarks in the lumbosacral spine area such as the iliac crest, sacroiliac joints, and intervertebral spaces to use as anatomical reference points for the injections. The skin is then cleaned with alcohol and betadyne to minimize the risk of infection. Some practitioners begin the treatment by injecting subcutaneous wheals of local anesthetic into the areas to be injected with prolotherapy solution to minimize patient discomfort [10].

Prolotherapy injections are often administered with 2.5 in., 20-gauge spinal needles to deliver a small bolus of solution into the following areas: posterior sacroiliac ligaments, iliolumbar ligaments, interspinous ligaments, supraspinous ligaments, and posterior intervertebral facet capsules. Some practitioners target ligaments that are tender to manual palpation or otherwise suspected of causing pain [11], whereas others prefer to inject all of the larger posterior ligaments that are accessible and possibly associated with CLBP [9]. To access these ligaments, the needle is typically inserted in the midline directly above an intervertebral space and oriented laterally to avoid accidentally injecting into the spinal canal. The needle is then inserted until the tip contacts bone and the plunger is partially withdrawn to confirm the absence of blood in the aspirate that would indicate possible blood vessel puncture. The desired bolus of solution—typically 0.5 to 2.0 ml—is then injected at each site [10]. Practitioners often target several ligaments from a single needle insertion point by reorienting the needle in situ. The total amount of solution injected during one session of prolotherapy depends on the number of structures that are targeted and the bolus delivered to each structure; 10 to 30 ml is common. Radiological guidance (eg, fluoroscopy) is seldom used in prolotherapy.

After the injection procedure, the patient is briefly observed and then sent home with instructions to perform repetitive spinal range of motion (ROM) exercises such as standing lumbar flexion and extension to maintain their flexibility as the acute inflammation produced by the injections results in lumbosacral stiffness and soreness over the next few days. Patients are also advised to use over-the-counter (eg, acetaminophen) or prescription (eg, hydrocodone) analgesics as needed for any increased pain in the

few days after the injections. Instructions are also given to avoid anti-inflammatory medication, because the acute inflammatory reaction provoked by this treatment is considered beneficial [11]. This injection procedure is typically repeated weekly, biweekly, or monthly until six to eight treatments have been administered. Treatment intervals are dictated by patient response to treatment and the recovery time required for any resulting acute inflammation to diminish before the next injection. Patients may also require periodic injections if pain relapses or reinjury occurs.

Practitioner, setting, and availability

Prolotherapy is mainly administered by medical or osteopathic physicians, though in rare instances a physician's assistant, nurse practitioner, or naturopath can administer injections where state licensure permits deep injections [12]. Practitioners who perform this treatment are expected to have advanced knowledge of spinal anatomy, including the attachment points for all connective tissue structures that may be injected, and the locations of any surrounding blood vessels or nerves that may be inadvertently injected. Extensive experience with spinal injections is usually recommended before learning prolotherapy and many clinicians who perform these treatments have specialized training in anesthesiology, pain management, or physical medicine and rehabilitation [12]. Additional postgraduate training specifically in prolotherapy is typically offered through continuing medical education courses sponsored by related organizations and medical schools, including the University of Wisconsin. Organizations involved in prolotherapy training include the American Association of Orthopaedic Medicine (AAOM) [13], American College of Osteopathic Sclerotherapeutic Pain Management (ACOSPM) [14], Hackett Hemwall Foundation [15], and American Institute of Prolotherapy [16].

In general, this treatment is performed in private clinics. It may occasionally be performed in a medical imaging facility if radiological guidance is required. A minority of practitioners prefer to administer oral or intravenous (IV) sedation before treatment to calm the patients and facilitate an otherwise uncomfortable procedure; this requires an ambulatory surgical center. This procedure is rarely performed in hospitals. Prophylactic oral analgesics may also be administered before the treatment instead of, or in addition to, sedation. Based on membership in related associations, it is estimated that there are approximately 500 to 1,000 practitioners offering this treatment in private practices in various cities throughout the United States. Groups such as the AAOM and ACOSPM maintain on-line membership directories with contact information of practitioners who offer this treatment.

Reimbursement

There is no current procedural terminology code specifically for this procedure listed in the latest edition of the current procedural terminology manual. Although it has not been determined whether it is acceptable to bill under these codes, practitioners occasionally use related injection codes to describe various aspects of this procedure, such as: 20550 (injection—single tendon sheath, or ligament), 20551 (injection—single tendon origin/insertion), 20552 (injection—single or multiple trigger point), 27096 (injection—procedure for sacroiliac joint), 64776 (injection—anesthetic agent and/or steroid, paravertebral facet joint or facet joint nerve), 99070 (supplies and materials—eg, list drugs, trays, supplies, or materials). The health care procedural coding system specifically for prolotherapy is M0076, which is not recognized for Medicare purposes. The cost of the procedure varies considerably by practitioner. A single treatment typically costs $250 to $500 excluding any required diagnostic testing, imaging, rehabilitative equipment, or treatment facility fees. A series of six treatments is therefore approximately $1,500 to $3,000. In the United States, this treatment is not directly covered by major medical insurance companies and is not generally covered by workers' compensation insurance. In some cases, it may be covered by automobile insurance medical payment riders.

A survey of patients with chronic pain (including CLBP) who had used prolotherapy reported that insurance coverage paid part of the cost in 88% of cases [8]. Patients had paid some cost out of pocket in 19% of cases; mean out-of-pocket costs in the past year for prolotherapy were $365 [8].

Regulatory status

Although individual ingredients such as dextrose and lidocaine are approved for injection by the FDA, they are not approved for this indication. Drug solutions injected during prolotherapy are typically prepared by compound pharmacies or individual practitioners, and thus not subject to regulation by the FDA.

Theory

Mechanism of action

As with many other treatments available for CLBP, the mechanism of action for prolotherapy is not well understood. This treatment was derived from sclerotherapy for varicose veins, where injected irritants provoke a localized acute inflammatory reaction, connective tissue proliferation, and lumen closure. In prolotherapy, four types of solutions have been identified according to their suspected mechanism of action: 1) osmotic (eg, hypertonic dextrose); 2) irritant/hapten (eg, phenol); 3) particulate (eg, pumice flour); and 4) chemotactic (eg, sodium morrhuate) [17]. Osmotics are thought to dehydrate cells, leading to cell lysis and release of cellular fragments, which attracts granulocytes and macrophages; dextrose may also cause direct glycosylation of cellular proteins [17]. Irritants possess phenolic hydroxyl group that are believed to alkylate

surface proteins, which renders them antigenic or damages them directly, attracting granulocytes and macrophages [17]. Particulates are believed to attract macrophages, leading to phagocytosis [17]. Chemotactics are structurally related to inflammatory mediators such as prostaglandins, leukotrienes, and thromboxanes, and are believed to undergo conversion to these compounds [17].

Other mechanisms of action for prolotherapy that do not involve localized acute inflammation have also been proposed. For instance, macrophages that respond to particulates are believed to secrete polypeptide growth factor, leading to fibroplasia [17]. Other possibilities include neurolysis of nociceptive fibers (denervation) because of the presence of phenol, lysis of connective tissue adhesions because of the volume of solution injected, and neovasculogenesis or neoneurogenesis during the inflammatory cascade [18].

A number of studies have been conducted in animals to elucidate the mechanism of action for solutions used in prolotherapy, including rat, guinea pig, and rabbit models [2]. In general, these studies involved ligament or tendon injections and histological or biomechanical examination of connective tissue. For example, rabbit medial collateral ligament mass, thickness, and weight-to-length ratio increased significantly 7 weeks after 5% sodium morrhuate injections [19]. However, there were no differences in traumatized rat Achilles tendon tensile strength 7 weeks after injection of various solutions used in prolotherapy (eg, dextrose, sodium morrhuate) [20]. Other studies reported changes consistent with local acute inflammation [2]. In three patients with CLBP of suspected ligamentous origin, biopsies of posterior sacroiliac ligaments were taken 3 months after 6 weekly injections with dextrose 12.5%, glycerin 12.5%, phenol 1.25%, lidocaine 0.25%, spinal manipulation, and repeated trunk flexion exercises [21]. Electron microscopy revealed a significant increase in cellularity and active fibroblasts, with a 60% increase in average fiber diameter [21].

Diagnostic testing required

Other than a thorough history and physical examination to rule out the possibility of serious pathology related to CLBP, no advanced diagnostic testing is required before prolotherapy. Plain film radiography is often used to evaluate spinal anatomy and pathology before injections.

Indications and contraindications

This treatment is generally used for nonspecific mechanical CLBP resulting from ligament or tendon injury from trauma, repetitive sprain injury, or collagen deficiency [21]. It is challenging to identify this subgroup of CLBP patients, as there are no direct, noninvasive methods of assessing lumbosacral ligament health. Diagnosis is therefore made on a clinical basis according to pain referral patterns, superficial ligament palpation, joint palpation, or history (eg, pain aggravated by maintaining a position for extended periods). The identity of anatomic structures responsible for nociception may be confirmed by observing temporary pain relief after local anesthetic injections, although the presumption that these findings can be used to identify structures to be injected with prolotherapy has yet to be validated. As is often the case with other interventions, the indication for prolotherapy may be CLBP that has failed to respond to other, more conservative treatments.

This treatment is considered to be contraindicated in patients with non-musculoskeletal pain (eg, referred visceral pain), metastatic cancer, systemic inflammation, spinal anatomical defects that preclude deep injections (eg, spina bifida), morbid obesity, inability to perform posttreatment ROM exercises, bleeding disorders, low pain threshold, chemical dependency, or whole body pain [2]. In addition, there is some indication from preclinical studies that very high doses of a prolotherapy solution containing dextrose 12.5%, glycerin 12.5%, phenol 1.0%, and lidocaine 0.25% may produce a temporary increase in hepatic enzymes such as alanine transaminase and aspartate aminotransferase [22]. Although these findings are preliminary, it may be prudent to not administer high doses of these solutions to patients with pre-existing hepatic conditions.

The ideal patient for this treatment is generally considered—purely on the basis of clinical opinion—an otherwise healthy adult aged 30 to 50 years with mechanical CLBP, no serious comorbidities, no psychopathology, signs and symptoms of lumbosacral ligament or tendon involvement, confirmation of pain structures by local anesthetic, and a positive but temporary response to manual therapy.

Evidence of efficacy

Review methods

A computerized search of Medline, Embase, and CINAHL was performed by combining the Cochrane Back Review group strategy for identifying controlled trials related to low back pain (LBP) with intervention specific index terms and free text: or Glucose/ad, tu, th [Administration & Dosage, Therapeutic Use, Therapy], or Glycerol/ad, tu, th [Administration & Dosage, Therapeutic Use, Therapy], or Phenol/ad, tu [Administration & Dosage, Therapeutic Use], or Lidocaine/ad, tu, th [Administration & Dosage, Therapeutic Use, Therapy], or Sclerosing Solutions/ad, tu, th [Administration & Dosage, Therapeutic Use, Therapy], or prolotherapy/ti, ab. Only articles published in English from 1997 to 2007 were considered. References of pertinent articles were also used to identify studies. Search results were combined and screened for eligibility by two independent reviewers (JM, JBS); conflicts were resolved by a third reviewer (SD). Studies were eligible if they were clinical practice guidelines, systematic reviews, or randomized controlled trials (RCTs) pertaining to prolotherapy for CLBP (longer than 3 months) and reported clinically relevant outcomes such as pain or function.

Table 1
Systematic reviews of prolotherapy for CLBP

Reference	[28]	[2]	[23]	[24]*
Review topic	Prolotherapy for CLBP	Prolotherapy for spinal pain	Prolotherapy for musculoskeletal pain	Prolotherapy for CLBP
Databases searched	Medline, Embase, CINAHL, Cochrane, SCI	Medline, Mantis, CINAHL, Cochrane, ExpandedAcademic ASAP	Medline, Embase, CINAHL, Applied and complementary medicine	Medline, Embase, CINAHL, Cochrane, AMED
Study eligibility	RCTs Quasi-RCTs	Clinical studies >5 patients English	Human subjects treated with prolotherapy	RCTs Quasi-RCTs
Quality assessment method	CBRG	Descriptive	Jadad	CBRG
Search results	Six RCTs Excluded One nonrandomized (Yelland, 2002) One crossover (Wilkinson,unpublished) 21 observational studies	Five RCTs 17 observational studies	Four RCTs Two CCTs	Seven RCTs Excluded One nonrandomized (Yelland, 2002) One crossover (Wilkinson, 2005)
RCTs reviewed	Ongley, 1987; Klein, 1993; Dechow, 1999; Yelland, 2004	Mathews, 1987; Ongley,1987; Klein, 1993; Dechow, 1999; Yelland, 2004	Ongley, 1987; Klein, 1993; Dechow, 1999; Yelland, 2004	Mathews, 1987; Ongley, 1987; Klein, 1993; Dechow, 1999; Yelland, 2004
Efficacy results	Protocols too different to combine results	Observational studies reported positive short-and long-term results	Observational studies reported subjective positive outcomes	Protocols very differentand results cannot be combined
	Quality of studies was high	Observational studies provided few details, had poor methodology, and were poorly reported	RCTs had poor patients election and operator differences	Possible dose-response relationship because two studies with negative results administered only 3×10 ml compared with three studies with 6×20–30 ml
	Results were mixed	RCTs had different protocols and could not be combined	Two RCTs had positive results and two RCTs had negative results	Two studies with cointerventions had positive results
	Positive results were noted in two studies with cointerventions	Two RCTs had positive results with 6×20–30 ml of solutions with dextrose/glycerin/ phenol/lidocaine, SMT, exercise, and other interventions	RCT results mixed because control groups improved	Three studies with prolotherapy alone had negative results
	Appears no better than control injections in two studies without cointerventions	Three RCTs had negative results with dextrose only, 3×10 ml, no SMT	CCTs mixed with one positive study and one negative study	
	Possible dose-response relationship because three injections seemed inferior to six			
	Phenol may be required for efficacy			
AEs	Most patients experience transient increase in pain and stiffness	Temporary (24–96 h) increase in pain and stiffness is common	Minimum AEs from observational studies	Temporary pain and stiffness were common
	Few cases of puncture headache	Six cases of puncture HA reported	Appears safe from RCTs	Cases of puncture HA reported
	No serious or permanent AEs reported	Other AEs were leg pain, nausea, diarrhea, and others		
Conclusions	No evidence that prolotherapy alone is beneficial for CLBP	Dextrose alone likely not beneficial for LBP Possible dose-response relationship Technique appears important Appears safe with newer dextrose/glycerin/ phenol/lidocaine solutions Safety comparable with other spinal injections		No evidence of efficacy for prolotherapy alone Evidence of partial prolonged pain relief for prolotherapy with exercise, SMT, and other interventions

SCI=science citation index; CBRG=Cochrane back review group; SMT=spinal manipulative therapy; CLBP=chronic low back pain; RCT=randomized controlled trial; LBP=low back pain; AE=adverse event.

* Update of Yelland, 2004 review.

Systematic reviews

We identified five reviews related to prolotherapy for CLBP [2,4,11,23,24]. One review was excluded because it failed to report its methodology and there was no indication that a systematic search approach had been followed [4]. The four included systematic reviews are summarized in Table 1 and briefly discussed below.

A review was published in *The Spine Journal* by our group in 2005 and identified the same five RCTs that were uncovered in this search [2]. Two of those RCTs had positive results and noted improvements in pain or disability with six weekly sessions injecting 20 to 30 ml of solutions containing dextrose/glycerin/phenol/lidocaine, spinal manipulation therapy (SMT), exercise, and other cointerventions [9,10]. Three RCTs had negative results and reported improvements but no differences between the prolotherapy and control: one study used only dextrose/lidocaine [11], one used only three sessions of dextrose/glycerin/phenol/lidocaine, and one study with a small sample size used dextrose/glycerin/phenol/procaine without SMT. The review concluded there was no evidence to support prolotherapy with dextrose alone. Furthermore, a dose-response relationship was postulated for solutions containing dextrose/glycerin/phenol/lidocaine, in which the lower doses (eg, 3×10 ml) appeared to be less effective than the larger doses (eg, 6×20 ml).

Rabago et al. [23] conducted a review on prolotherapy for musculoskeletal pain, including CLBP and identified four of the five RCTs mentioned in the previous review. Two of those studies were generally positive, and two were generally negative. Authors of that review noted that the RCTs had poor patient selection and operator differences in treatment procedures.

Two reviews on prolotherapy injections for CLBP have been published by the Cochrane Collaboration, one by Yelland et al. [11] in 2004, and an update by Dagenais et al. [24] in 2007. Study eligibility for both reviews included RCTs and quasi-RCTs on prolotherapy for CLBP, and both reviews assessed study quality using Cochrane Back Review group criteria. The efficacy results of prolotherapy for CLBP reported in the updated review [24] were as follows: prolotherapy protocols vary a great deal and results cannot be combined; there is a possible dose-response relationship with prolotherapy, because negative results were noted in two RCTs with lower doses of the administered drug (eg, 3×10 ml) compared with three studies with higher doses (eg, 6×20–30 ml); two RCTs with prolotherapy administered with cointerventions had positive results, whereas three RCTs with prolotherapy administered alone had negative results. Thus, the authors concluded that there is no evidence of efficacy for prolotherapy alone, whereas there is evidence of partial prolonged pain relief for prolotherapy combined with exercise, SMT, and other interventions.

Randomized controlled trials

We identified six RCTs related to prolotherapy for CLBP [9–11,25–27]. One RCT was excluded because it was a crossover and it was not possible to attribute reported results to prolotherapy [27]. The details from these five RCTs are given in Table 2 and briefly discussed below.

In an RCT by Mathews et al. [25], 22 individuals with CLBP were randomly assigned to receive prolotherapy (n=16) or control (n=6) injections. Prolotherapy injections consisted of a solution containing dextrose 10%, glycerin 10%, phenol 1%, and procaine 0.3%. There were three sessions injecting 10 ml every 2 weeks into lumbosacral ligaments. Control injections consisted of a solution containing 0.05% procaine, also with three sessions injecting 10 ml every 2 weeks into tender spots. Outcomes were assessed at 2 weeks and 1, 3, 6, and 12 months and included a six-point numerical rating scale (1–4 designated ''not recovered'' and 5–6 designated ''recovered''), pain intensity (visual analog scale [VAS]), and medication use. At 3 months, 10 out of 16 patients in the experimental group (63%) were recovered, compared with 2 out of 6 (33%) in the control group. There were no significant differences between the groups at the other time points.

In an RCT by Ongley et al. [9], 82 individuals with CLBP were randomly assigned to receive prolotherapy (n=40) or control (n=42) injections, along with various cointerventions. Prolotherapy injections for the experimental group consisted of a solution containing dextrose 12.5%, glycerin 12.5%, phenol 1.25%, lidocaine 0.25%. There were six sessions injecting 20 ml every week into lumbosacral ligaments with IV sedation. Cointerventions included 50 mg triamcinolone injection into the gluteus medius and SMT for the experimental group, lidocaine 0.5% injection and sham SMT for the control group, and standing lumbar flexion-extension stretching exercises for both groups. At 6 months, there were statistically significant differences ($p<.05$) for all outcomes in favor of the experimental group. Additionally, 35 out of 40 (88%) patients in the experimental group had greater than 50% improvement in disability score at 6 months, compared with 16 out of 41 (39%) patients in the control group ($p<.05$). There were 15 out of 40 (38%) patients in the experimental group versus 4 out of 41 (10%) patients in the control group with a disability score of 0 at 6 months ($p<.05$). Radiating leg pain present at baseline was resolved in 10 out of 12 (83%) patients in the experimental group versus 2 out of 12 (17%) patients in the control group ($p<.05$) at 6 months. Given the various cointerventions, however, it is difficult to partition the positive outcomes of the experimental group to the prolotherapy injections.

In an RCT by Klein et al. [10], 79 individuals with CLBP were randomly assigned to receive prolotherapy (n=39) or control (n=40) injections. Prolotherapy injections for the experimental group consisted of a solution containing dextrose 12.5%, glycerin 12.5%, phenol 1.2%, lidocaine 0.5%. There were six sessions injecting 30 ml every week into lumbosacral ligaments, facets, and SI joints, along with IV sedation and lidocaine wheals. Control injections consisted of a solution containing saline 0.45% and lidocaine 0.25%, along with IV sedation. Outcomes were

Table 2
Randomized controlled trials of prolotherapy for CLBP

Reference	[25]	[9]	[10]	[26]	[11]
Inclusion criteria	18–60 Symptoms >3 mo Local backache and local tenderness	21–70 LBP >1 y Unresponsive to nonsurgical care	21–60 LBP >6 mo Failed to respond to conservative treatments	18–71 Mechanical LBP >6 mo Referred by GP	21–70 LBP >50% days past 6 mo Failed conservative care
Exclusion criteria	Abnormalities or complicating problems	<4 modified RM >25% over ideal bodyweight Coronary artery disease Debilitating medical conditions Disability pay Insulin dependent DM Litigation pending Pregnancy Unsettled work comp claim	Acute exacerbation of chronic pain >40 lbs over ideal bodyweight Pregnancy Prior L/S laminectomy Serious medical conditions Significant hip joint arthritis Unresolved work comp	>20 kg over ideal bodyweight Evidence nerve root entrapment Pregnancy Severe coexisting disease Unresolved litigation	>3 Waddell nonorganic signs Acute exacerbation BMI >33 (women), >35 (men) Cancer Fibromyalgia Hip OA/aseptic necrosis Inflammatory arthritis Lumbar stenosis Pregnancy Prior prolotherapy Prior spinal surgery Radiculopathy Unresolved litigation/work comp claim
Number randomized	22	82	79	74	110
Experimental	16	40	39	36	54 (28 exercise, 26 normal activities)
Control	6	42	40	38	56 (27 exercise, 29 normal activities)
Experimental group injections	Dextrose 10% Glycerin 10% Phenol 1% Procaine 0.3% 3×10 ml every 2 wk into lumbosacral ligaments	Dextrose 12.5% Glycerin 12.5% Phenol 1.25% Lidocaine 0.25% 6×20 ml weekly into lumbosacral ligaments IV sedation	Dextrose 12.5% Glycerin 12.5% Phenol 1.2% Lidocaine 0.5% 6×30 ml (max) weekly into lumbosacral ligaments, facets, SI joints IV sedation Lidocaine wheals	Dextrose 12.5% Glycerin 12.5% Phenol 1.2% Lidocaine 0.5% 3 × 10 ml into L4–L5 ligaments with single needle insertion point IV sedation	Dextrose 20% Lidocaine 0.2% a maximum of 6×30 ml every 2 wk into lumbosacral ligaments
Control group injections	Procaine 0.5% 3×10 ml every 2 wk into tender spot	Saline 0.9% 6×20 ml weekly into lumbosacral ligaments	Saline 0.45% Lidocaine 0.25% IV sedation	Saline 0.45% Lidocaine 0.5%	Saline 0.9% ×30 ml (max) every 2 wk into lumbosacral ligaments
Cointerventions	Paracetamol 500 mg PRN	First intervention (Experimental) Maximum of 60 ml lidocaine into lumbosacral ligaments 50 mg triamcinolone in gluteus medius Spinal manipulation	First intervention was triamcinolone injections into irritable foci if needed		Both groups Analgesics, heat, general activity Daily zinc, manganese, beta car otene, pyridoxine, vitamin C No NSAIDs
	Spinal corset PRN	First intervention (Control) 10 ml lidocaine into lumbosacral ligaments Sham spinal manipulation	Discontinued NSAIDs/analgesics		Exercise subgroup: Standing lumbar flexion/ extension 4×/day

(*Continued*)

Table 2 (*continued*)

Reference	[25]	[9]	[10]	[26]	[11]
	Posture/back care education	Both groups Standing lumbar flexion/extension 150×/day Return to full ADL Standing lumbar flexion/ extension 4×/day Walking 1 mile 5×/week	Acetaminophen/ice as needed		
Outcomes	(1 to 4—not recovered, 5 to 6—recovered)	Modified RM (+9 questions from Waddell)	Roland Morris	McGill pain questionnaire	Days reduced activity
	Six-point VAS	Pain diagram	VAS	Modified Schober test	Medication use
	Medication use	VAS	Pain grid	Modified somatic perception questionnaire	Modified RM
	Numerical rating scale		L/S dynamometer	Modified Zung	Pain diagram
			Proportion > 50% improvement in VAS/RM	ODI	Satisfaction with treatment
				Pain grid	SF-12
				VAS	VAS
Follow-up	1 mo	1 mo	6 mo	1 mo	2.5 mo
	3 mo	3 mo		3 mo	4 mo
	6 mo	6 mo		6 mo	6 mo
	12 mo				12 mo
					24 mo
Results	Recovered at 3 mo Experimental: 10 out of 16 Control: 2 out of 6		Proportion > 50% improvement in pain or disability Experimental: 30 out of 39 Control: 21 out of 40	No SS differences between groups at any point	No SS differences between groups at any point
	No SS changes in other outcomes at other time points		Change in pain grid Experimental: 5.28 Control: 3.87		
			No SS changes in VAS disability, dynamometer		
AEs	No cases of increased pain	Both groups reported pain and stiffness for 12–24 h	One lumbar puncture HA in each group with no sequelae	Transient back pain	Increased back pain and stiffness
		Experimental: 4 out of 40; Control: 1 out of 41 had menstrual irregularities, likely from triamcinolone			Headache, nausea/diarrhea, thoracic pain, other symptoms
		Control: 1 out of 41 HA and cough			Four lumbar puncture HA
		No differences in laboratory assessment of toxicology (CBC, sed rate, urinalysis, chem panel, thyroid function)			Four leg pain with radiculopathy
Comments/ conclusions			Subgroup analysis excluding 13 patients (8 Experimental, 5 Control) with irritable foci who received triamcinolone reported SS changes favoring Experimental group for all outcomes		

assessed at 6 months included the Roland Morris Disability Questionnaire, pain intensity (VAS), pain grid, lumbar ROM, lumbar isometric strength, and the proportion of subjects with greater than 50% improvement in disability and pain intensity. Both groups had significant improvement ($p<.05$) in pain intensity, pain grid scores, and disability at 6 months. When defining success with treatment as a 50% improvement in pain intensity or disability, 30 out of 39 (77%) patients in the experimental group versus 21 out of 40 (53%) in the control group were successful ($p<.05$).

In an RCT by Dechow et al. [26], 74 individuals with CLBP who were referred by a general practitioner were randomly assigned to receive prolotherapy (n=36) or control (n=38) injections. Prolotherapy injections for the experimental group consisted of a solution containing dextrose 12.5%, glycerin 12.5%, phenol 1.2%, and lidocaine 0.5%. There were three sessions injecting 10 ml every week into L4–L5 ligaments with single needle insertion point, along with IV sedation. Control injections consisted of a solution containing saline 0.45% and lidocaine 0.5%. Outcomes were assessed at 1, 3, and 6 months and included the McGill pain questionnaire, ROM (modified Schober test), modified somatic perception questionnaire, modified Zung questionnaire, Oswestry Disability Index, pain grid, and pain intensity (VAS). At each follow-up time point, there were no significant differences between the treatment and control groups for any of the outcomes.

An RCT by Yelland et al. [11] was designed to concurrently assess the efficacy of prolotherapy and exercise. In this study, 110 individuals with CLBP were randomly assigned to one of four groups: prolotherapy injections with exercise (n=28) or without exercise (n=26) or control injection with exercise (n=27) or without exercise (n=29). Prolotherapy injections consisted of a solution containing dextrose 20% and lidocaine 0.2%. There were six sessions injecting a maximum of 30 ml every 2 weeks into lumbosacral ligaments. Control injections consisted of a solution containing saline 0.9%. Exercise consisted of standing lumbar flexion/extension stretches 4×/day, whereas the nonexercise groups continued normal activity. Outcomes were assessed at 2.5, 4, 6, 12, and 24 months. At each follow-up time point, there were no significant differences in any of the outcomes among the groups. In their analyses, the authors disregarded assignment to exercise or normal activity and compared subjects who received prolotherapy with those who received saline injections.

Ongoing studies

Preclinical studies are currently under way by our group to support a planned Phase 1 clinical trial of a drug solution commonly used in prolotherapy for CLBP.

Harms

The most common side effect related to prolotherapy is a temporary (12–96 hours postinjection) increase in pain and/or stiffness at the injection site, which is consistent with drug's purported mechanism of action (ie, acute inflammation) [12]. In a recent survey of prolotherapy practitioners (n=171) who were members of the AAOM or ACOSPM, side effects with the highest median estimated prevalence were pain (70%), stiffness (25%), and bruising (5%) following prolotherapy for spinal pain. Other side effects reported in the literature were increased transient leg pain, headache, nausea, diarrhea, minor allergic reactions, and other transient symptoms [12].

Adverse events (AEs) related to prolotherapy for CLBP include mainly needlestick injuries similar to those reported with other common spinal injection procedures [12]. There are previous reports of severe headache indicative of lumbar puncture, leg pain with neurological features, disturbed sleep because of psychological trauma from injections, and severe cough. No fatalities related to this treatment have been reported in the literature for a period of almost 50 years in which this treatment has been offered [2]. Rare AEs include pneumothorax, disc injury, meningitis, hemorrhage, and nerve damage. In a recent survey of practitioners (n=171) who had each provided a median of 2,000 prolotherapy treatments for spinal pain, 470 AEs were reported [12]. Of these 470 AEs, 70 were considered severe: 65 required hospitalization and 5 resulted in permanent injury. The vast majority (80%) of AEs were related to needle injuries rather than drug toxicity. They included spinal headache (n=164), pneumothorax (n=123), nerve damage (n=54), hemorrhage (n=27), spinal cord insult (n=7), and disc injury (n=2).

Practitioners often report that the predictors of negative outcomes with prolotherapy are similar to other treatments for CLBP and include tobacco use, obesity, inability to perform posttreatment ROM exercises, serious comorbidities, psychopathology, and an incorrect diagnosis.

Summary

Prolotherapy is one of a number of treatments recommended for the treatment of CLBP. It has a prolonged history of use, a reasonable but not proven theoretical basis, a low complication rate, and conflicting evidence of efficacy. A possible dose-response effect or the combination with other interventions such as SMT may explain the conflicting results of RCTs. Two of the RCTs in which prolotherapy was administered using six weekly injections of 20 to 30 ml dextrose/glycerin/phenol/lidocaine with SMT and exercise had positive results, suggesting this particular intervention protocol is worth considering for patients with CLBP who are refractory to other approaches. At this time there is no evidence of efficacy for prolotherapy injections alone without cointerventions.

There is sufficient interest and utilization of this procedure to warrant further investigation. Future studies are needed to support or refute the positive results obtained in some of the prior RCTs while addressing some of the

methodological weaknesses by minimizing differences between the intervention and control groups. Other studies are also needed to establish the safety of common prolotherapy solutions, and determine the optimal dose and number of injection sessions required.

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