



**TITLE:** Prolotherapy for the Treatment of Chronic Low Back Pain

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## PROLOTHERAPY FOR THE TREATMENT OF CHRONIC LOW BACK PAIN

### INTRODUCTION

The California Technology Assessment Forum is requested to review the scientific evidence for the use of prolotherapy for the treatment chronic low back pain.

### BACKGROUND

Chronic musculoskeletal pain is common, frequently under-reported, and inadequately treated. Its evaluation and treatment is often frustrating for both the patient and the clinician. Patients with chronic pain may become isolated from friends and family, lose their jobs, and develop depression. Despite its prevalence, chronic pain is often poorly understood and inconsistently managed by health care providers (Devereaux, 2003).

Low back pain is a common disorder, ranking second only to upper respiratory tract infection as a reason for visits to physicians in the United States (Deyo and Weinstein, 2001). Back pain may originate from many spinal structures, including ligaments, facet joints, the vertebral periosteum, the paravertebral musculature and fascia, blood vessels, the annulus fibrosus, and spinal nerve roots. Perhaps most common are musculoligamentous injuries and age-related degenerative processes in the intervertebral disks and facet joints, spinal stenosis, and disk herniation. It is often not possible to attribute the problem to any specific disease or pathologic lesion (Deyo and Weinstein, 2001) and the association between symptoms and imaging results is weak (Devereaux, 2003). Occasionally, however, back pain is caused by a serious systemic disorder such as cancer or infection. There is not good evidence for most of the common treatment approaches to chronic back pain. Structured exercise programs are often cited as being the most effective treatment for chronic back pain (Deyo and Weinstein, 2001).

Treatment of chronic low back pain may consist of pharmacologic and/or non-pharmacologic approaches. Pharmacologic treatments generally include non-steroidal anti-inflammatory drugs and opioid or non-opioid analgesics and antidepressants. Nonpharmacologic techniques such as acupuncture, massage, and relaxation also may be helpful to the patient with chronic pain. Epidural corticosteroid injections can provide short-term relief of sciatica but do not improve functional status or reduce the need for surgery. Corticosteroid injections into facet joints are not effective for chronic low back pain (Carette *et al.*, 1991). Spinal manipulation and physical therapy are alternative treatments for symptomatic relief among patients with subacute low back pain, but their effects are limited (Andersson *et al.*, 1999)

## Prolotherapy

Prolotherapy is a non-surgical injection procedure used to treat connective tissue injuries of the musculoskeletal system that have not healed by rest or conservative therapy. Proponents of prolotherapy propose that pain is related to activation of pain receptors in tendon or ligament tissues, which are sensitive to stretching and pressure; it is thought that pain results from this ligamentous laxity.

Prolotherapy refers to the injection of sclerosing solutions into joints, muscles, or ligaments to promote a healing response in small tears and weakened tissue, with the goal of alleviating back pain and improving function. With the prolotherapy procedure, the substance injected into the soft tissue causes a localized tissue reaction leading to an inflammatory response. The wound - healing cascade is thus triggered resulting in fibroplasia and collagen deposition. "Prolo" is short for proliferation, because the treatment is thought to lead to the proliferation of new ligament tissue in areas where it has become weak. Prolotherapy is also referred to as sclerosant therapy, sclerotherapy, regenerative injection therapy, "proliferative" injection therapy and nonsurgical ligament reconstruction. Prolotherapy has been used in pain management and treatment of numerous conditions, including back pain, neck pain, headaches, and joint pain (knee and foot). More recently, it has been reported to promote improvement in anterior cruciate ligament laxity (Reeves and Hassanein, 2003).

Three categories of proliferants have been used: irritants (e.g., phenol, tannic acid, and quinine), osmotic shock agents (e.g., glucose, glycerin, ZnSO<sub>4</sub>), and chemotactic agents (e.g., sodium morrhuate). The most common solutions are dextrose based. For example, to achieve a 12.5% concentration, dilution is made with a local anesthetic in 1:3 proportions. These are then mixed with a small concentration of local anesthetic before being injected into tender areas as identified by the patient, and broad tendinous attachments. Prolotherapy generally involves a series of injections, ranging from three to 30 (average 4 to 10), depending on the condition and the individual being treated. The injection series may cover two to six months with injections at two to three week intervals. Patients are instructed that they should not expect results for about six weeks. After treatment, the expectation is that the pain will be permanently alleviated, but some practitioners advocate a "booster" injection every year or so after the initial series (Linetsky *et al.*, 2004).

The concept of treating musculoskeletal pain by creating new scar or connective tissue has been reported to date back to Hippocrates' use of a hot poker to treat the chronically painful and unstable shoulders of javelin throwers (Mooney, 2003). Various sclerosing agents have been used over the past 100 years to treat varicosities and to repair hernias non-surgically. In the 1950's, a general surgeon named Hackett began using sclerosing agents to strengthen ligaments, and changed the name to "proliferant therapy" or prolotherapy (Mooney, 2003).

In addition to chronic lower back pain, prolotherapy has been utilized for a number of painful musculoskeletal conditions including headache (Abraham, 1997), neck pain (Kayfetz, 1963) and arthritis (Reeves and Hassanein,

2000a; Reeves and Hassanein, 2000b). In a randomized placebo-controlled trial of prolotherapy in osteoarthritic finger joints, Reeves and Hassanein (2000a) recruited 13 patients to receive active treatment and 14 patients to serve as controls. To qualify, patient's joints needed to meet radiographic criteria of OA and be painful for at least six months. They received injections at time zero, two and four months and outcomes were assessed at six months. Injections were given along the joint line and not into the joint itself. They found that pain at rest and with grip improved in both groups at six months. More improvement was seen in the experimental group, but the difference did not reach statistical significance. In another randomized controlled trial, Reeves and Hassanein (2000b), report on prolotherapy for knee OA with or without ACL laxity. At six months (after three injections of Dextrose solution vs. saline), both groups showed considerable improvement in VAS scores for pain, as well as in pain with walking and stair use. These results may encourage further investigation in the future.

The potential risks and complications of prolotherapy are similar to that of any soft tissue injection with the additional potential problems from the sclerosing agent. Possible side effects that may last a few days to a couple weeks include pain and swelling at the site of injection, pain secondary to nerve irritation, allergic reaction to the proliferant or anesthetic, headache, and increased musculoskeletal pain or discomfort. Rare complications include nerve damage or paralysis, pneumothorax and spinal fluid leak.

**TA Criterion 1:                   The technology must have the appropriate regulatory approval.**

Dextrose, glycerine and phenol are all FDA approved drugs.

**TA criterion 1 is met**

**TA Criterion 2:                   The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.**

The published peer reviewed literature examining the use of prolotherapy in the treatment of chronic back pain consists of four randomized clinical trials of prolotherapy for chronic lower back pain (Yelland *et al.*, 2004; Dechow *et al.*, 1999; Klein *et al.*, 1993; Ongley *et al.*, 1987). In addition, there are numerous case reports and patient testimonials in print and on-line (e.g. <http://www.prolotherapy.com>) that are beyond the scope of this report.

Outcomes assessed in these trials include pain intensity and unpleasantness as measured by a visual analogue scales (VAS), pain rulers and pain diagrams; days of reduced activities; medication use; and the physical and mental health components of the SF-12. Patients generally were followed for up to two-years.

Most studies of prolotherapy to date are small and have limited statistical power. There is sufficient evidence to evaluate the safety and efficacy of prolotherapy for treatment of lower back pain; other uses of prolotherapy have not been adequately evaluated.

## **TA criterion 2 is met**

Levels of Evidence: 1, 5.

## **TA Criterion 3: The technology must improve the net health outcomes.**

### Patient Benefits

#### Prolotherapy for chronic low back pain

In the largest study of prolotherapy to date, Yelland *et al.*, 2004 report on a randomized controlled trial of patients conducted in a university general practice clinic in Australia. They recruited patients aged 21-70 years with low back pain present on more than half the days over six months and a failure of conservative treatment to give sustained pain relief. Patients with spinal stenosis, osteoarthritis of the hip, inflammatory arthritis, and BMI > 33-35 were excluded. Patients were randomized to prolotherapy vs. control and received injections of glucose and lignocaine (0.2%) in 5 mL of water, or injections containing normal saline only. The primary guide for injection sites was tenderness in ligaments and broad tendinous attachments of the L-S spine and pelvic girdle. A maximum of 10 sites were treated at each visit, and if no improvement was noted by the fifth visit (by 10 weeks) the deeper interosseous sacroiliac ligaments on the affected side or sides were also treated. For all participants, analgesics, heat and general activity were recommended for post-injection pain and stiffness. Participants were also randomized into either a special exercise or usual exercise program. There were significant reductions in mean pain intensity and disability scores from baseline in all groups from 2.5 months through the end of the trial. There were no significant differences between the groups. At 12 months, the proportions of all participants who rated their pain and disability as better than at enrollment were 0.76 and 0.68 respectively, again with no significant differences between the groups. At 12 months, the proportions of participants who achieved at least 50% reductions of pain in each group were glucose-lignocaine: 0.46; saline: 0.36; exercise: 0.41 and normal activity: 0.39. These proportions were not statistically significantly different. Adverse effects generally were minor and did not differ between the four groups. Adverse effects included: increased low back pain (0.88), increased back stiffness (0.76), increased leg pain (0.60) and headache (0.59), among others. In this study, prolotherapy was not more effective than injections of normal saline, and the addition of exercise did not alter the outcomes. All participants demonstrated marked and sustained improvement in their pain and disability.

Dechow *et al.*, 1999 report on a randomized, double-blind, placebo controlled trial of three, once weekly injections of dextrose-glycerine-phenol with lignocaine vs. saline plus lignocaine in patients with mechanical back pain of more than six months duration. Injections were given by an orthopedic physician blinded to the solution used and the study protocol. Seventy-four patients were recruited; none dropped out. Outcome measures included the short-form McGill Pain Questionnaire, a pain VAS and present pain intensity score, the modified Zung depression inventory and a disability scale. Patients were assessed at one, three and six months following treatment. The authors report that there were no statistically significant differences between the placebo and treatment groups for any measure over the six-month follow-up. A few subjects reported a transient increase in back pain following the injections. There were no significant adverse reactions and no differences between the control and treatment groups. In sum, this study found that sclerosing injections are of no greater benefit than placebo in the treatment of patients with chronic low back pain.

Klein *et al.*, 1993 report on a randomized double-blind trial of six weekly injections of proliferant solution (dextrose, glycerine, phenol and 0.5% lidocaine) vs. saline and lidocaine. Patients were sedated prior to the injections, which were directed into the posterior sacroiliac and interspinous ligaments, fascia, and joint capsules of the low back from L-4 to the sacrum. Patients with "hyperirritable foci" were also injected with 20 mg of triamcinalone prior to randomization and were also given a spinal manipulation treatment. All patients were instructed in an exercise program. After randomization there were 40 patients in each of the two groups. The main outcome measure was 50% improvement in pain and/or disability scores. Overall, both treatment groups improved markedly from baseline. In the prolotherapy group, 30 of 39 patients reported at least 50% improvement in pain or disability scores compared to 21 of 40 in the lidocaine control group ( $p = 0.042$ ), at six months. Differences between groups at the six-month follow-up favored the proliferant group in improvement in pain scores ( $p = 0.025$ ), visual analog scores ( $p = 0.056$ ), and disability scores ( $p = 0.068$ ). The authors report that side effects were minor and did not differ between the groups but specific data is not presented. Since phenol is a potent chemical irritant, it may produce recognizable sensations in the intervention patients thus leading to potential unblinding of the intervention. The authors conclude that this study, "suggests that the (proliferant) injections are an important component of the treatment regimen" . . . "even though the statistical significance was only borderline". The clinical significance of the relatively minor differences between the groups also appears to be "borderline", at best. Overall, it is not possible to conclude from this study that prolotherapy should be part of the armamentarium for the treatment of chronic lower back pain.

In an early study, Ongley *et al.*, 1987 report on results from a randomized blinded trial of 81 patients with chronic low back pain. Forty patients received forceful spinal manipulation and weekly injections of dextrose-glycerine-phenol solution plus 0.5% lignocaine; forty-one received weekly saline plus lignocaine for six weeks. At six months, an improvement of more than 50% was found in 35/40 of the proliferant group vs. 16/41 of the controls ( $p < 0.003$ ). Visual analog pain scores and pain diagrams were also significantly more improved in the experimental group.

However, it is not possible to distinguish between the benefits of spinal manipulation alone and the additional benefits derived from prolotherapy.

In sum, recent research has not been able to replicate earlier findings that prolotherapy is superior to placebo for treatment of chronic low back pain. In all studies to date there is a significant response to placebo, a common phenomenon when studying medical problems with significant psycho-social sequelae. It is therefore not possible to conclude from the published literature that prolotherapy is superior to placebo injection for the treatment of chronic low back pain.

### **TA criterion 3 is not met**

#### **TA Criterion 4:           The technology must be as beneficial as any established alternatives.**

Alternatives to prolotherapy for the treatment of chronic low back pain not amenable to surgical intervention include nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, exercise, and epidural injections. Unfortunately, few treatments for chronic low back pain have been scientifically validated (Devereaux, 2003). Few randomized trials have been undertaken for nonspecific low back pain. Nonsteroidal antiinflammatory drugs (NSAIDs) are effective for symptom relief, as are some muscle relaxants (van Tulder, Koes and Bouter, 1997).

In general, medication for symptomatic relief should be prescribed on a regular schedule rather than on an as-needed basis. Exercise programs can reduce pain and improve function in patients with chronic low back pain (Frost *et al.*, 1998). In a recent review, Linton and van Tulder (2001) found that of the many interventions recommended for the prevention of back problems, only exercise was shown to be effective. Graded activity exercise regimens have been found to be more effective than placebo in reducing the number of days absent from work due to low back pain (Staal *et al.*, 2004). However, it is difficult for patients to maintain a consistent exercise program. About one-third of patients with chronic low back pain suffer from depression and the use of antidepressant medication reduces symptoms in these patients (Atkinson *et al.*, 1998). Many patients with chronic back pain are treated with long-term opioid therapy. A small, randomized trial showed that opioids have a greater effect on pain and mood than NSAIDs; however, opioids did not improve activity levels, and in a third of subjects they caused side effects such as drowsiness, headache, constipation, and nausea (Deyo and Weinstein, 2001). There are several popular complimentary and alternative therapies for the treatment of chronic low back pain; few are supported by randomized trials. One recent review did find support for the use of massage for persistent low back pain and found that acupuncture was not effective (Cherkin *et al.*, 2001). There is no evidence from clinical trials or cohort studies that surgery is effective for patients who have chronic low back pain unless they have sciatica, pseudoclaudication, or spondylolisthesis (Deyo and Weinstein, 2001). There is limited evidence that epidural steroid injection with local anesthetic benefits pain and function in low back pain (Bernstein, 2001). For many patients, complete relief of

symptoms may be unrealistic, and therapeutic goals may need to be refocused on optimizing daily function (Deyo and Weinstein, 2001).

To date, prolotherapy has not been shown to be as beneficial as the alternatives for the treatment of chronic low back pain.

**TA criterion 4 is not met.**

**TA Criterion 5: The improvement must be attainable outside the investigational settings.**

Prolotherapy has not been found to be effective under investigational settings.

**TA criterion 5 is not met.**

## **RECOMMENDATIONS OF OTHERS**

### **Blue Cross Blue Shield Association (BCBSA)**

The BCBSA Technology Evaluation Center has not reviewed this topic.

### **Centers for Medicare and Medicaid Services (CMS)**

The CMS coverage manual states:

35-13 PROLOTHERAPY, JOINT SCLEROTHERAPY, AND LIGAMENTOUS INJECTIONS WITH SCLEROSING AGENTS--NOT COVERED

The medical effectiveness of the above therapies has not been verified by scientifically controlled studies. Accordingly, reimbursement for these modalities should be denied on the ground that they are not reasonable and necessary as required by §1862(a)(1) of the law.

### **American Association of Orthopaedic Medicine (AAOM)**

A representative of the AAOM attended the meeting and testified in support of the use of prolotherapy for the treatment of low back pain.

### **California Orthopaedic Association (COA)**

A representative of the COA was not able to attend the meeting. The COA does not have a formal opinion/position regarding the use of prolotherapy.

## CONCLUSION

Low back pain is a common disorder, ranking second only to upper respiratory tract infection as a reason for visits to physicians in the United States. Many patients have no anatomic abnormality that can explain their symptoms. There is some evidence that patients with chronic pain may undergo changes in the central nervous system that may perpetuate the pain in the absence of anatomic problems or ongoing injury (Coderre *et al.*, 1993). This is an area of ongoing research.

Prolotherapy has been proposed as a treatment for chronic low back pain that has not responded to traditional therapy. Prolotherapy refers to the injection of sclerosing solutions into joints, muscles, or ligaments to promote a healing response in small tears and weakened tissue, with the goal of alleviating back pain and improving function. It is generally a safe procedure with mainly minor and transient side effects reported in the literature.

To date, there have been four randomized controlled trials of prolotherapy for the treatment of chronic low back pain and two RCT's of prolotherapy for the treatment of chronic pain secondary to osteoarthritis. In the majority of these studies, prolotherapy was no better than placebo in treating pain. Only in the first RCT of prolotherapy for chronic low back pain (Ongley *et al.*, 1987) was prolotherapy clearly better than placebo for treatment of chronic low back pain. The explanation for the positive results over placebo reported in this study is unclear; it has been hypothesized that these results may be due in part to patient selection, and/or differences in the protocol in which the placebo group received a smaller dose of local anesthetic compared with the prolo group (10 ml of 0.5% lignocaine compared with 60 ml 0.5%), and the prolo group had an initial spinal manipulation while controls had a sham manipulation. In the largest and most recent trial (Yelland *et al.* 2004) prolotherapy was not more effective than injections of normal saline, and the addition of exercise did not alter the outcomes. All participants demonstrated marked and sustained improvement in their pain and disability. As one editorial stated, it may be that "putting a needle into someone's back is beneficial independent of what, if anything, is injected (Loesser, 2004)

In sum, only one early study (Ongley *et al.*, 1987) was able to demonstrate conclusively that prolotherapy was significantly superior to placebo for treatment of chronic low back pain. Subsequent research has not been able to replicate this finding. It is therefore not possible to conclude from the published literature that prolotherapy is superior to placebo injection for the treatment of chronic low back pain.

## RECOMMENDATION

It is recommended that prolotherapy for the treatment of chronic low back pain does not meet California Technology Assessment Forum TA criteria 3-5.

*The California Technology Assessment Forum approved the recommendation as presented.*

June 9, 2004

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