SPINE Volume 29, Number 1, pp 9–16

Prolotherapy Injections, Saline Injections, and Exercises for Chronic Low-Back Pain: A Randomized Trial

Michael J. Yelland, FRACGP, FAFMM,* Paul P. Glasziou, PhD, FRACGP,*
Nikolai Bogduk, MD, DSc,† Philip J. Schluter, BSc(Hons), PhD,* and
Mary McKernon, RN, Grad Dip Nurs Admin*

Objectives. To assess the efficacy of a prolotherapy injection and exercise protocol in the treatment of chronic nonspecific low back pain.

Design. Randomized controlled trial with two-by-two factorial design, triple-blinded for injection status, and single-blinded for exercise status.

Setting. General practice.

Participants. One hundred ten participants with nonspecific low-back pain of average 14 years duration were randomized to have repeated prolotherapy (20% glucose/0.2% lignocaine) or normal saline injections into tender lumbo-pelvic ligaments and randomized to perform either flexion/extension exercises or normal activity over 6 months.

Main outcome measures: Pain intensity (VAS) and disability scores (Roland-Morris) at 2.5, 4, 6, 12, and 24 months.

Results. Follow-up was achieved in 96% at 12 months and 80% at 2 years. Ligament injections, with exercises and with normal activity, resulted in significant and sustained reductions in pain and disability throughout the trial, but no attributable effect was found for prolotherapy injections over saline injections or for exercises over normal activity. At 12 months, the proportions achieving more than 50% reduction in pain from baseline by injection group were glucose-lignocaine: 0.46 versus saline: 0.36. By activity group these proportions were exercise: 0.41 versus normal activity: 0.39. Corresponding proportions for >50% reduction in disability were glucose-lignocaine: 0.42 versus saline 0.36 and exercise: 0.36 versus normal activity: 0.38. There were no between group differences in any of the above measures.

Conclusions. In chronic nonspecific low-back pain, significant and sustained reductions in pain and disability occur with ligament injections, irrespective of the solution injected or the concurrent use of exercises. [Key words: low back pain, randomized controlled trial, injections, exercise, prolotherapy, sclerotherapy] **Spine 2004;29:9–16**

Prolotherapy is a treatment for chronic nonspecific low-back pain that involves a protocol of ligament injections, exercises, and vitamin and mineral supplements. It is based on the premise that back pain results from weakened ligaments and that these ligaments can be strengthened by the injection into them of irritant proliferant solutions.[12,17,14,20] These solutions variously contain phenol, glycerine, or hypertonic glucose, mixed with local anesthetic, and aim to induce inflammation and deposition of collagen fibers in the weak ligaments. There is limited histologic evidence of thickening of sacroiliac ligaments in association with a reduction in low-back pain scores and increased lumbar range of motion using all these solutions combined.[14] The supplementary regimen of exercises and oral vitamins and minerals ostensibly promote collagen growth to induce optimal strengthening of the treated ligaments.

The anecdotal and experimental evidence are contradictory. Testimonies to the effectiveness of prolotherapy include one from the former Surgeon General of the United States, C. Everett Koop, MD,[16] ". . .I have been a patient who has benefited from prolotherapy. Having been so remarkably relieved of my chronic disabling back pain, I began to use it on some of my patients." The few controlled trials of prolotherapy have provided mixed results. One trial reported negative results.[4] In another, the results were borderline-positive.[15] The one trial with clearly positive results was confounded by the use of co-interventions such as spinal manipulation and injection of tender gluteal muscles with corticosteroid.[19] The efficacy of prolotherapy injections and the associated exercise program for low-back pain, therefore, has not been established.

Phenol has been a classic constituent of proliferant solutions, and at concentrations of 1.2% has been promoted as safe.[19] Many practitioners prefer to use an alternative solution of hypertonic glucose and lignocaine only,[7] although there is no histologic or clinical trial evidence of its efficacy. The present trial was undertaken to assess the efficacy and safety of glucose/lignocaine prolotherapy injections and exercises in a randomized, controlled trial. The null hypothesis was that prolotherapy injections and exercises would be no more effective than the control treatment.

Materials and Methods

The trial was conducted in a university general practice clinic with the approval of the University of Queensland medical research ethics committee. From April to November 2000, potential participants were recruited from the southeast Queens-

*Centre for General Practice and School of Population Health, University of Queensland, Brisbane, Australia and †Newcastle Bone and Joint Institute, University of Newcastle, Royal Newcastle Hospital, Australia.
Acknowledgment date: January 22, 2003. Acceptance date: April 28, 2003.
The legal regulatory status of the device(s)/drug(s) that is/are the subject of this article is not applicable in the authors' country.
Federal, Foundation, and Professional Organization funds were received to support this work. No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this article.
Address correspondence and reprint requests to Michael Yelland, Inala Health Centre General Practice, 64 Wirraway Pde, Inala, Brisbane, Queensland, Q 4077, Australia. E-mail: myelland@bigpond.com

land community through general practice and physiotherapy referrals, a letter to clinic patients, clinic posters, newspaper articles, and advertisements, as well as radio and television interviews. After telephone interview to screen out clearly ineligible patients, a musculoskeletal physician performed a clinical assessment on potentially suitable patients. A full blood examination and erythrocyte sedimentation rate, and a radiograph of the lumbosacral spine (if not performed in the preceding 12 months), were obtained to screen for spinal pathology.

Inclusion criteria were age 21 to 70 years, low-back pain present on more than half the days in the past 6 months, modified Roland-Morris disability questionnaire[21] score more than three, and failure of conservative treatment(s) to give sustained pain relief. Exclusion criteria were acute exacerbation of pain, lumbar spinal stenosis or radiculopathy, osteoarthritis or aseptic necrosis of the hip, cancer, inflammatory arthritis, previous spinal surgery or prolotherapy, body mass index more than 33 for women and 35 for men (making injections technically difficult), unresolved litigation or workers' compensation claims, fibromyalgia,[31] more than three of Waddell's nonorganic signs of back pain,[29] and pregnancy or intended pregnancy. All participants were given extensive written and verbal information about trial treatments and their potential benefits and risks before giving their written consent for treatment and 12-month follow-up. Consent for a 24-month follow-up was subsequently obtained from 96 participants.

Assignment. The trial followed a two-by-two factorial design. Using a computer-generated random number system, with block sizes of four and eight, participants were randomized to receive either the index injections or control injections, and randomized to an exercise program or normal activity. The index injections contained 20% glucose/0.2% lignocaine (with 4 ml 50% glucose, 1 ml 2% lignocaine, and 5 ml water in each 10-ml syringe). The control injections contained normal (0.9%) saline. The randomization schedule was kept locked in the clinic pharmacy, where pharmacists or doctors not involved in the participants' care accessed it and prepared the injection solutions.

Masking. Syringes were covered with white paper and administered with gloved hands. The activity status of participants was known to the treating physician but was concealed by a code number from the staff who assessed outcomes. Participants were instructed not to discuss their activity status with outcome assessors. The security of masking was checked at the 4-month visit by asking the participant, treating physician, and outcome assessor to nominate the injection group allocation and the outcome assessor to nominate the activity group allocation.

Sample Size. Sample size calculations using a binomial proportions test were based on the results of a previous trial using saline injections[19] and on a pilot study by the authors.[32] To detect a response rate of 40% versus 70% for greater than 50% reduction in pain, with a power of 80% and an alpha of 0.05, a group size of 50 was required. Allowing for a 10% dropout rate, a sample size of 110 was chosen.

Protocol. The chief investigator treated all participants, closely following a protocol described by Dhillon.[7] The primary guide for injection sites was tenderness in ligaments and broad tendinous attachments (entheses) of the lumbosacral spine and pelvic girdle, with consideration of the patterns of local and referred pain.[12] Injections were performed through an anesthetized wheal of skin over each site after first contacting bone to confirm their position. Approximately 3 ml solution was infiltrated at each site and a maximum of 10 sites treated at each visit. If no improvement was noted by the fifth session, 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 postinjection pain and stiffness, but the use of anti-inflammatory medications was discouraged. All participants were supplied with a daily supplement of zinc 30 mg, manganese 22.5 mg, beta-carotene 3 mg, pyridoxine 15 mg, and vitamin C 1,000 mg for the 6-month treatment period.

Exercise group participants were taught two sagittal loading exercises to be performed in standing–alternating flexion and extension of the hips to midrange with the spine held straight, and flexion of the lumbar spine with the hips stationary. Ten repetitions of each exercise were to be performed four times daily for 6 months. All participants were encouraged to continue all their pretrial activities and exercises.

Injections occurred every 2 weeks until six treatments were completed. At 4 and 6 months, injections were repeated only if there had been a partial response to treatment. Between 6 and 12 months, further review was arranged on request for relapses in pain lasting more than 1 week and further injections were administered if indicated. The major outcome assessment was set for 12 months with a supplementary assessment at 24 months.

Evaluation. At each visit, visual analogue scales for pain and disability, any exacerbation of back/leg pain and stiffness, and any new symptoms were recorded. In the exercise group, exercise technique and compliance were checked and rated from zero (no exercises performed) to three (exercises performed at least daily). Compliance with vitamin/mineral supplements was also checked at each visit and by tablet count at 6 months.

Primary outcome measures were the usual pain intensity in the past week, recorded on a 100-mm visual analogue scale (VAS),[13] and a 23-item modified Roland-Morris disability questionnaire.[21,24] Secondary measures of outcome included a VAS of pain unpleasantness in the past week,[13] days of reduced activities in the past 28 days,[6] medication use, the physical and mental health component summary scales of the SF-12,[30] and a pain diagram. From the pain diagram, the area of pain in the lower half of the body was quantified using a transparent grid.[2]

The previous week's consumption of analgesics and other drugs was assessed as[18,10]: 0 = no analgesic use; 1 = nonnarcotic analgesics/antidepressants/muscle relaxants up to four times per week; 2 = nonnarcotic analgesics/antidepressants/muscle relaxants more than four times per week; 3 = morphine or analogues up to four times per week; 4 = morphine or analogues more than four times per week.

Outcome forms were completed by participants and checked by a trained independent assessor. Pain intensity and disability scores were measured at baseline and 2.5, 4, 6, 12, and 24 months. Pain unpleasantness, pain diagram, days of reduced activities, and SF-12 scores were measured at baseline and 4, 6, 12, and 24 months. Medication use was measured at baseline and 4, 6, and 12 months and crosschecked with a record of prescriptions filled and a count of tablets remaining at 4 and 6 months.

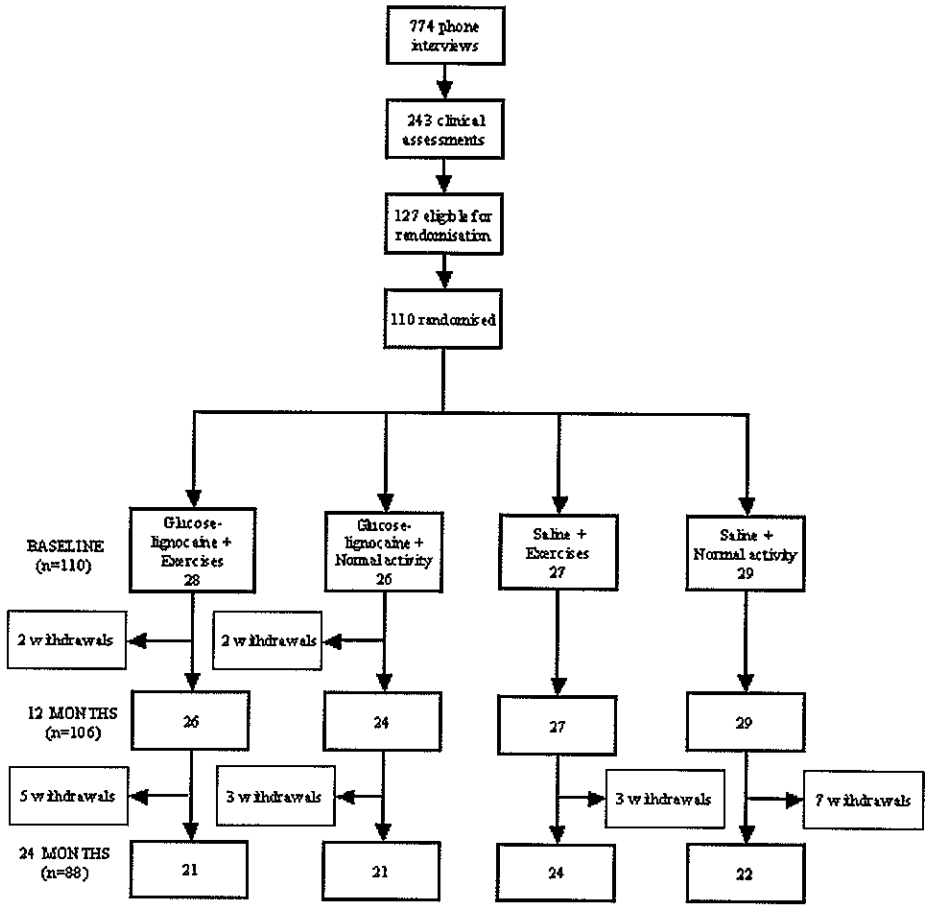

Figure 1. Flow chart of inquirers and participants throughout the trial.

To give a participant-specific benchmark for success of treatment, participants were asked at enrollment to nominate the minimum acceptable percentage reduction in pain and in disability to make treatment worthwhile. A global assessment of changes in pain and disability was made at 12 months. Satisfaction with treatment was also measured at this time using the satisfaction scale from the North American Spine Society low-back pain outcome assessment instrument,[3] with higher scores indicating greater satisfaction.

Statistical Analysis. Data analysis was planned before completion of the trial and was performed on an intention to treat basis, with the statistician blinded to group allocation. SAS version 8.2 software[2,5] was used, with separate analyses by injection group and by activity group. Demographic and clinical variables at enrollment are expressed as frequencies and means plus or minus standard deviation (SD). Minimum clinically important differences are expressed as medians. Outcome data are expressed as means (95% CI) in graphs and means ± SD in Tables. Numbers in each group achieving reductions in pain and disability of greater than 50% were calculated. Student's t test was used to assess within group differences over time and Fisher's exact test for between group differences at each point in time. All tests were two-tailed with significance set at $P < 0.05$.

The primary outcome measures were further analyzed using a mixed effects model with a quadratic function for time. This was performed for complete cases only and with imputation for missing values by carrying the last value forward.[1]

■ Results

Recruitment

Over a 7-month period, 774 people inquired about the trial, 243 of whom were potentially eligible after telephone interview, and underwent clinical assessment. Of these, 127 satisfied the recruitment criteria. Seventeen people declined to participate, leaving 110 who consented to participate. The ratios of participants-to-inquirers for each source of recruitment were: television, 50:375; newspaper, 23:126; general practitioners, 13:62; radio, 11:100; letter or invitation, 7:20; and other, 6:53.

Trial Profile

Participant flow through the trial is displayed in Figure 1. Of the 110 participants randomized, 109 (99%) completed assessments at 6 months, 106 (96%) at 1 year, and 88 (80%) at 2 years. Five participants did not complete the baseline course of six treatments because of pain (2), work commitments (2), or facet joint injections from another physician (1). Of these five, two were in the glucose-lignocaine/exercise subgroup, two were in the saline/exercise subgroup, and one was in the saline/normal activity subgroup. They nevertheless completed all follow-up assessments.

Table 1. Demographic and Clinical Characteristics of Participants by Injection Group and by Activity Group at Inception and of Those Who Declined Participation

	Participants (n = 110)				
	Injection Group		Activity Group		
	Glucose-lignocaine (n = 54)	Saline (n = 56)	Exercise (n = 55)	Normal activity (n = 55)	Nonparticipants (n = 17)
Frequency (%)					
Men	32 (59.3)	31 (55.4)	31 (56.4)	32 (58.2)	10 (58.8)
Presence of leg pain	24 (44.4)	23 (41.1)	26 (47.3)	21 (38.2)	10 (58.8)
Smokers	18 (33.3)	15 (26.8)	16 (29.1)	17 (30.9)	3 (17.6)
Working	23 (42.6)	31 (55.4)	29 (52.8)	25 (45.5)	10 (58.8)
Heavy manual work	2 (3.7)	8 (14.3)	5 (9.1)	5 (9.1)	2 (11.7)
Lumbar X-ray findings associated with pain[27]	34 (63.0)	38 (67.9)	35 (63.6)	37 (67.3)	7 (41.2)
Mean (SD)					
Age at entry	51.5 (10.6)	49.4 (10.4)	50.0 (9.8)	50.9 (11.2)	47.9 (13.3)
Duration of pain (y)	14.8 (10.9)	13.8 (9.3)	14.6 (9.6)	14.1 (10.6)	9.6 (7.7)
Body mass index	26.6 (3.8)	25.8 (3.8)	26.2 (3.7)	26.2 (3.9)	26.9 (4.3)
Anxiety score (0–10)	4.8 (2.3)	5.0 (2.1)	5.1 (2.1)	4.7 (2.2)	—
Depression score (0–10)	3.2 (2.2)	3.1 (1.9)	3.3 (2.1)	2.9 (1.9)	—
Number of past therapies for back pain[¥]	4.0 (1.5)	4.3 (1.8)	4.3 (1.7)	4.0 (1.6)	3.3 (1.0)
VAS of pain intensity (0–100)	51.9 (19.3)	55.0 (20.7)	54.6 (19.8)	52.3 (20.3)	50.7 (20.6)
Roland-Morris disability score (0–23)*	13.7 (5.0)	14.3 (4.5)	13.0 (5.1)	15.0 (4.3)	—
Pain unpleasantness	53.4 (22.4)	55.6 (24.3)	55.7 (23.2)	53.5 (23.5)	—
Pain diagram grid score	9.1 (7.5)	12.3 (10.3)	11.5 (8.5)	9.9 (7.9)	—
Medication score	1.2 (1.3)	1.4 (1.4)	1.3 (1.3)	1.3 (1.4)	—
Days of reduced activity in past 28 days	8.2 (9.2)	6.5 (8.5)	6.7 (8.5)	8.0 (9.2)	—
SF-12 Physical Component Summary score	35.2 (9.9)	32.1 (7.1)	35.4 (7.9)	31.9 (6.9)	—
SF-12 Mental Component Summary score	47.6 (12.7)	49.6 (12.4)	47.0 (12.0)	50.3 (12.9)	—

* $p = 0.03$ for exercise group vs. normal activity group.
¥ $p = 0.004$ for all participants vs. nonparticipants.

Group Comparability

At baseline the only significant differences in the mean (SD) of major demographic and clinical characteristics were the disability scores for exercise and normal activity groups [13.0 (5.1) versus 15.0 (4.3); $P = 0.03$] and the number of past therapies used for back pain by participants and nonparticipants [4.2 (1.6) versus 3.3 (1.0); $P = 0.004$] (Table 1). Otherwise there were no significant baseline differences between the two injection groups, between the two activity groups, among the four-injection/activity subgroups, between participants and nonparticipants or between trial completers and noncompleters.

Per participant, the mean (SD) number of treatments was 7.1 (1.5). Per treatment, 7.3 (1.7) sites and a total volume 23.6 (4.1) ml of solution were injected. In these variables, there were no statistically significant differences between groups. Mean (SD) compliance rates for exercises in the exercise group was 2.6 (0.5), with those who received normal saline having slightly but significantly better compliance (2.7 ± 0.3) than those receiving glucose-lignocaine (2.5 ± 0.6). More than 80% of all groups had greater than 80% compliance rates with vitamin and mineral supplements.

Masking

Injection group allocation was correctly guessed by the treating physician in 26 cases, by the outcome assessors in 12 cases and by the participants in 14 cases. Incorrect guesses were made by the treating physician in 21 cases, by the outcome assessors in 14 cases and by the participants in 13 cases. Activity group allocation was correctly guessed by the outcome assessors in six cases and incorrectly guessed in two cases. The remainder of guesses was "do not know" responses.

Primary Outcomes

There were significant reductions in mean pain intensity and disability scores from baseline in all groups from 2.5 months through until the end of the trial (Figures 2 and 3). At 12 months, these ranged from 26% to 44% for pain and from 30% to 44% for disability; however, at no point were there significant differences between injection groups or between activity groups. Mixed model analysis of these scores revealed significant decreases, with a linear or quadratic trend over time for all treatment groups ($P < 0.001$), but no significant differences between 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, with no differences between treatment groups. The median of minimum acceptable reductions to make treatment worthwhile was 25% for pain and 35% for disability. The proportion of all participants who achieved their nominated minimum acceptable reductions at 12 months was 0.55 for pain and 0.54 for disability, also with no differences between groups.

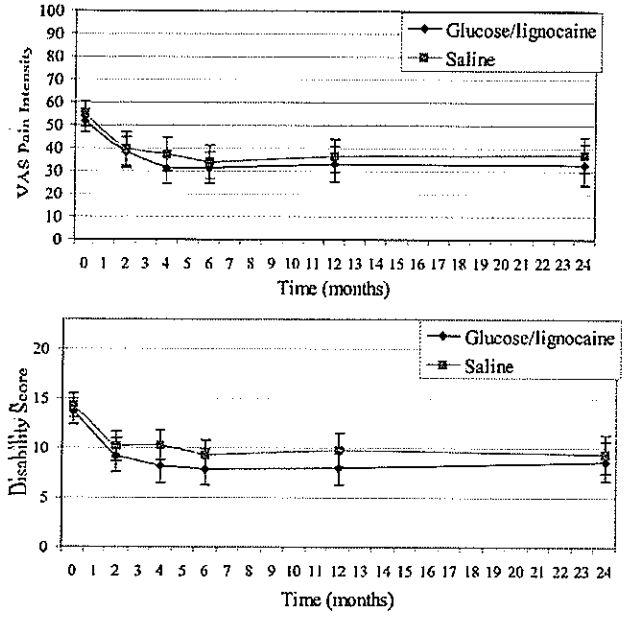

Figure 2. Mean (95% CI) pain intensity and disability scores by injection group. Values for all follow-up points are significantly less than values at inception ($P < 0.05$)

At 12 months, the proportions of participants who achieved at least 50% reduction 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 significantly different statistically. The corresponding proportions for at least 50% reduction in disability were glucose-lignocaine: 0.42, saline: 0.34, exercise: 0.36, normal activity: 0.38, with there being no statistically significant differences between these proportions. A greater proportion of patients in the glucose-lignocaine group (0.47) than in the saline group (0.28) achieved

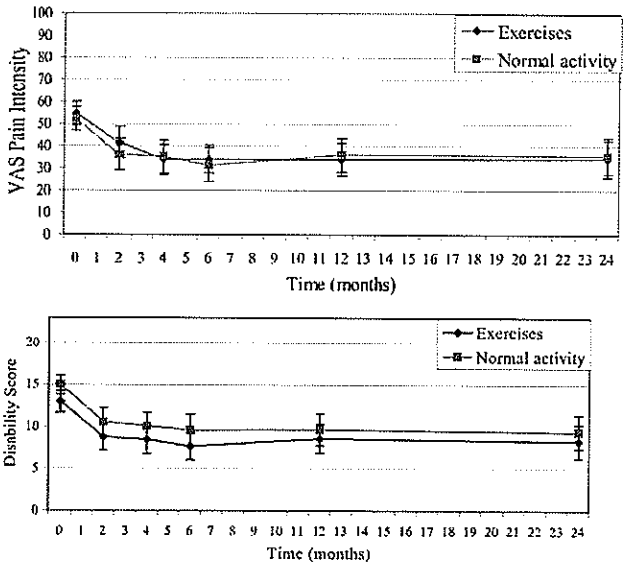

Figure 3. Mean (95% CI) pain intensity and disability scores by activity group. Values for all follow-up points are significantly less than values at inception ($P < 0.05$)

greater than 50% reduction in disability at 4 months but no such differences occurred at any other time.

At 12 months, the proportion of the total sample with zero pain scores was 0.20 and with zero disability scores was 0.09, but there were no differences between the proportions in each group achieving these outcomes. The only significant difference occurred at 6 months with the group proportions with zero disability being 0.15 for glucose-lignocaine and 0.02 for saline.

Secondary Outcomes

There were no changes from baseline levels for medication scores or mental health scores (Table 2). All groups exhibited similar and significant improvements in pain unpleasantness, days of reduced activity, and the PCS-12 over the 24 months. Some differences occurred between groups at baseline (Table 1) and at 12 months in pain grid scores and PCS-12 scores, but the change scores were similar (Table 2).

At the 12-month assessment, treatment satisfaction levels were similar in all groups, ranging from 3.6 to 4.0 on a 6-point scale. Similar proportions in all groups noticed an improvement in their pain (0.75–0.78) and in their ability to perform activities (0.64–0.68) over the first 12 months.

Potential adverse effects reported at least once during the trial (and the proportion of participants reporting them) included: increased low-back pain (0.88), increased back stiffness (0.76), increased leg pain (0.60), headache (0.59), nausea/diarrhea (0.42), thoracic spinal pain (0.10), and all other symptoms (0.56). The incidence of potential adverse effects did not differ between groups. The median duration of increased back pain was 4 days, increased leg pain 5 days, and increased back stiffness 5 days. Four participants had severe headaches (suggestive of lumbar puncture) within 1 day of injection treatments, but these all resolved within 1 week. Four participants developed leg pain with neurologic features and CT or MRI scan evidence of a lumbar radiculopathy. Symptoms resolved in three of them with conservative treatment and in one with a laminectomy. One participant had Bell's palsy 2 months into treatment, but this resolved completely over 3 weeks. One participant underwent a nephrectomy for renal carcinoma during the trial period. One participant with major depression was an inpatient in a psychiatric unit at the beginning of the trial and intermittently throughout most of the trial. There were no deaths during the trial period.

■ Discussion

Two major results warrant discussion. Clearly, prolotherapy was not more effective than injections of normal saline, nor did adding exercises improve the outcomes. In essence, there were no attributable effects of the glucose-lignocaine and exercise components of the prolotherapy protocol. Nevertheless, participants exhibited marked and sustained improvements in their pain

Table 2. Change Scores (SE) for Primary and Secondary Outcome Measures From Baseline for Injection Groups

	One Year			Two Years		
	Glucose-lignocaine	Saline	*P*	Glucose-lignocaine	Saline	*P*
Primary outcome measures						
Pain intensity	18.6 (3.2)	18.4 (4.0)	0.96	18.4 (4.0)	16.4 (4.2)	0.93
Disability score	5.5 (0.9)	4.5 (0.8)	0.85	4.9 (1.0)	4.2 (0.9)	0.60
Secondary outcome measures						
Pain unpleasantness	20.9 (3.4)	19.1 (4.0)	0.74	17.3 (4.4)	15.5 (4.3)	0.77
Pain diagram grid score	2.7 (1.1)	1.7 (1.8)	0.63	−0.2 (1.5)	1.3 (1.8)	0.52
Medication score	−0.1 (0.2)	−0.1 (0.2)	0.96	—	—	—
Days of reduced activity in last 28 days	3.2 (1.2)	2.4 (1.4)	0.66	2.5 (1.6)	1.8 (1.3)	0.75
SF-12 Physical Component Summary score	5.5 (8.1)	6.0 (10.1)	0.757	1.4 (1.3)	3.3 (1.3)	0.30
SF-12 Mental Component Summary score	0.6 (13.6)	−0.2 (12.4)	0.752	−0.8 (1.8)	1.1 (1.8)	0.48

Positive values indicate improvement in the measure and negative values indicate deterioration.

and disability, even with saline injections and normal activity. The basis for this response is intriguing.

As a test of prolotherapy for chronic low-back pain, the three previous trials[19,15,4] had cohorts with similar baseline levels of pain and disability as our trial but differed in some other respects. They all used a phenol/glycerine/glucose/lignocaine proliferant and had 6 months of follow-up, whereas we used a glucose-lignocaine proliferant and had 2 years of follow-up. With an average duration of back pain of 14 years, our cohort becomes the most chronic group studied to date.

The first of these trials, by Ongley et al,[19] investigated the effect of several interventions concurrently. Their proliferant group had an initial manipulation under local anesthesia, while their saline controls had a sham manipulation under a lower dose of local anesthesia. All participants had six injection treatments and did exercises for 6 months. The proportion of participants with greater than 50% reductions in pain/disability scores at 6 months was significantly higher in the proliferant group at 0.88 than in the saline controls at 0.39. Their findings have been construed elsewhere as evidence of efficacy of manipulation (rather than prolotherapy)[28] and as the cumulative neurolytic effect of phenol on treated ligaments.[15]

Prompted by these uncertainties, the second trial by Klein et al[15] tested the phenol/glycerine/glucose (sclerosant) components of the solution by having lignocaine controls. All participants had an initial manipulation under local anesthesia followed by six injection treatments and performed exercises for 6 months. Both groups showed significant improvements in mean pain or disability scores at 6 months, but the differences between groups did not quite reach significance. However, the proportion with greater than 50% reductions in pain or disability scores at 6 months was significantly higher in the proliferant group at 0.77 than in the lignocaine controls at 0.53. The results of the control group resemble the proportion with greater than 50% reduction in pain alone in our trial at 0.50 for glucose-lignocaine and 0.49 for saline. However, we used a more superficial and targeted injection technique than that used by Klein. This observation invites speculation that the same results may be achieved with even more superficial injections.

Finally, Dechow, et al[4] used a lignocaine control group, gave only three injection treatments with much lower volumes of injection solution than in the other trials and used no manipulation or exercises. This showed no change in mean pain or disability in either group over 6 months. This may suggest that the number of injections may have been the active component in our trial. Alternatively it may have been a nonspecific effect of increased contact with the clinic.

Table 3. Change Scores (SE) for Primary and Secondary Outcome Measures From Baseline for Activity Groups

	One Year			Two Years		
	Exercise	Normal activity	*P*	Exercise	Normal activity	*P*
Primary outcome measures						
Pain intensity	20.5 (3.8)	16.5 (3.5)	0.43	18.0 (3.8)	16.6 (4.5)	0.80
Disability score	4.8 (0.9)	5.1 (0.8)	0.75	3.9 (0.9)	5.2 (0.9)	0.36
Secondary outcome measures						
Pain unpleasantness	22.4 (4.0)	17.5 (3.4)	0.35	16.7 (3.9)	16.1 (4.9)	0.92
Pain diagram grid score	3.6 (1.2)	0.7 (1.7)	0.16	0.2 (1.9)	1.0 (1.3)	0.74
Medication score	−0.1 (0.1)	−0.1 (0.2)	0.93	—	—	—
Days of reduced activity in last 28 days	2.8 (1.2)	2.7 (1.3)	0.96	2.0 (1.3)	2.3 (1.6)	0.89
SF-12 Physical Component Summary score	5.8 (10.4)	5.8 (7.8)	0.975	1.2 (1.2)	3.6 (1.4)	0.17
SF-12 Mental Component Summary score	3.2 (12.0)	−2.8 (13.2)	0.0172	−0.2 (1.9)	0.5 (1.7)	0.79

Positive values indicate improvement in the measure and negative values indicate deterioration.

Our trial was the first to test the contribution of simple sagittal loading exercises to the overall effect. The absence of effect, despite good levels of compliance, contrasts with the positive results of more demanding, supervised, and effective regimens used in other trials of exercise.[9,5] This may reflect the absence of a muscle strengthening and general fitness component in the exercises.

Using a meticulous recording protocol, we documented a much higher incidence of transient, minor adverse effects than in previous trials. These adverse effects were equally common in all groups but restrict the indications for prolotherapy to a point at which other less invasive or irritating treatments have failed.

This trial's success rates in reducing pain and improving disability are at least as good as those reported for spinal cord stimulation,[26] surgery,[8] or multidisciplinary treatment[11] for patients with low-back pain of shorter duration. How might our results be explained? Given the lack of a noninjection control group, attributing the effect to a specific element of the prolotherapy protocol is difficult. The observed improvements may constitute no more than a regression to the mean, *i.e.*, patients enroll in a trial when they have periods of severe pain, but their apparent response represents no more than a natural reversion to lesser levels of pain. Although at enrollment 42% of participants described their pain as worsening gradually, all trial applicants with acute exacerbations of their pain were excluded from enrolling. Alternatively, the effect may lie in the needle rather than the specific injection solution, by a counterirritation effect, shown elsewhere to inhibit pain in humans.[23] The effect of prolonged vitamin and mineral supplements on low-back pain has not been studied, although some beneficial effect on wound healing has been demonstrated.[22] Finally, patients with chronic back pain might simply respond to confident treatment from a caring practitioner, irrespective of the biologic nature of the treatment provided. Further experimental and clinical studies are needed to elucidate the attributable effects of the other components of the prolotherapy protocol not studied here.

■ Key Points

- Previous trials of prolotherapy, a controversial injection and exercise protocol for chronic low-back pain that aims to strengthen weakened ligaments by repeatedly inflaming them with irritant solutions, have shown conflicting results.
- Significant and sustained reductions in chronic low-back pain and disability were observed with glucose/lignocaine injections for 2 years, but these were no different to saline control injections.
- There was no contribution of exercises to the efficacy of the prolotherapy protocol.

Acknowledgments

The trial was funded by grants from the Australian General Practice Evaluation Program, the Australian Association of Musculoskeletal Medicine, and the Musculoskeletal Research Foundation of Australia. The contributions of the participants and of Karen McCann, Dr. Robert Michael, Tilly Mylonas, and the staff of the Inala Health Center General Practice in the conduct of the trial are gratefully acknowledged.

References

1. Bennett DA. How can I deal with missing data in my study? *Aust N Z J Public Health* 2001;25(5):464–469.
2. Bryner P. Extent measurement in localised low-back pain: a comparison of four methods. *Pain* 1994;59:281–285.
3. Daltroy LH, Cats Baril WL, Katz JN, et al. The North Am spine society lumbar spine outcome assessment Instrument: reliability and validity tests. *Spine* 1996;21:741–749.
4. 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.
5. Deyo RA, Walsh NE, Martin DC, et al. A controlled trial of transcutaneous electrical nerve stimulation (TENS) and exercise for chronic low back pain. *N Engl J Med* 1990;322:1627–1634.
6. Deyo RA, Battie M, Beurskens AJHM, et al. Outcome Measures for Low Back Pain Research—A Proposal for Standardized Use. *Spine* 1998;23: 2003–2013.
7. Dhillon GS. Prolotherapy in Lumbo-Pelvic Pain. *Aust Musculoskel Med* 1997;2:17–19.
8. Fritzell P, Hagg O, Wessberg P, et al. 2001 Volvo Award Winner in Clinical Studies: Lumbar fusion versus nonsurgical treatment for chronic low back pain: a multicenter randomized controlled trial from the Swedish Lumbar Spine Study Group. *Spine* 2001;26:2521–2532.
9. Frost H, Lamb SE, Klaber Moffett JA, et al. A fitness programme for patients with chronic low back pain: 2-year follow-up of a randomised controlled trial. *Pain* 1998;75:273–279.
10. Gallon RL. Perception of Disability in Chronic Back Pain Patients: A Long-Term Follow-Up. *Pain* 1989;37:67–75.
11. Guzman J, Esmail R, Karjalainen K, et al. Multidisciplinary rehabilitation for chronic low back pain: systematic review. *BMJ* 2001;322:1511–1516.
12. Hackett GS, Hemwall GA, Montgomery GA. *Ligament and tendon relaxation treated by prolotherapy.* Oak Park, Illinois: Hemwall, GA; 1993:94–100.
13. Huskisson EC. Visual Analogue Scales. In: Melzack R, ed. *Pain Measurement and Assessment.* New York: Raven Press; 1983:33–37.
14. Klein RG, Dorman TA, Johnson CE. Proliferant injections for low back pain: histologic changes of injected ligaments and objective measurements of lumbar spine mobility before and after treatment. *J Neurol Orthop Med Surg* 1989;10:123–126.
15. 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.
16. Koop CE. Prolotherapy articles. American Association of Orthopaedic Medicine. URL: http://www.kalindra.com/prolotherapy.htm.
17. Liu YK, Tipton CM, Matthes RD, et al. An in situ study of the influence of a sclerosing solution in rabbit medial collateral ligaments and its junction strength. *Connect Tissue Res* 1983;11:95–102.
18. Manniche C, Asmussen K, Birgitte L, et al. Low Back Pain Rating Scale: validation of a tool for assessment of low back pain. *Pain* 1994;57:317–326.
19. Ongley MJ, Klein RG, Dorman TA, et al. A new approach to the treatment of chronic low back pain. *Lancet* 1987;2:143–146.
20. Ongley MJ, Dorman TA, Eek BC, et al. Ligament instability of knees: a new approach to treatment. *Man Med* 1988;3:152–154.
21. Patrick DL, Deyo RA, Atlas SJ, et al. Assessing Health-Related Quality of Life in Patients With Sciatica. *Spine* 1995;20:1899–1909.
22. Pories WJ, Henzel JH, Rob CG, et al. Acceleration of wound healing in man with zinc sulphate given by mouth. *Lancet* 1967;1:121–124.
23. Reinert A, Treede R, Bromm B. The pain inhibiting pain effect: an electrophysiological study in humans. *Brain Res* 2000;862:103–110.
24. Roland M, Morris R. A Study of the Natural History of Back Pain—Part 1: Development of a Reliable and Sensitive Measure of Disability in Low-Back Pain. *Spine* 1983;8:141–144.
25. SAS Institute Inc. The SAS System for Windows. 8.2 ed. Cary, NC: SAS Institute; 2002.
26. Turner JA, Loeser JD, Bell KG. Spinal cord stimulation for chronic low back pain: a systematic literature synthesis. *Neurosurgery* 1995;37:1088–1095.

27. van Tulder MW, Assendelft WJ, Koes BW, et al. Spinal radiographic findings and nonspecific low back pain. A systematic review of observational studies. *Spine* 1997;22:427–434.
28. van Tulder MW, Koes BW, Bouter LM. Conservative treatment of acute and chronic nonspecific low back pain. A systematic review of randomized controlled trials of the most common interventions. *Spine* 1997;22:2128–2156.
29. Waddell G, McCulloch JA, Kummel E, et al. Nonorganic physical signs in low-back pain. *Spine* 1980;5:117–125.
30. Ware JE, Kosinski M, Keller SD. SF-12: How to score the SF-12 physical and mental health summary scales. Third ed. Lincoln, RI: Quality Metric Incorporated; 1998.
31. Wolfe F, Committee MC. The American College of Rheumatology 1990 — Criteria for the Classification of Fibromyalgia. *Arthritis Rheum* 1990;33: 160–172.
32. Yelland M, Yeo M, Schluter P. Prolotherapy injections for chronic low back pain: results of a pilot comparative study. *Aust Musculoskel Med* 2000;5:20–23.

Point of View

John D. Loeser, MD

This is a beautifully conceived and executed study in all respects. I congratulate the authors on publishing such a wonderful research project. It has several strengths but raises an interesting challenge for further research. First, the authors have succeeded in showing that prolotherapy is no better than injecting saline in the treatment of chronic low-back pain. Second, exercise therapy does not have advantages over regular activity. Both pain scores and disability scores were the same in all four groups of patients. Two sets of oxen have been gored by this study. I expect that those who have an emotional or financial commitment to prolotherapy will raise arguments based on patient selection, how the therapy was administered, or methods of evaluation of outcomes. Others will argue that the wrong kinds of physical therapy were used. The authors have managed to construct a study that has met all of the criteria for excellence. I doubt that there are any hidden flaws that will in any way mitigate the outcomes.

The interesting challenge is why did all of these patients, in either arm of the prolotherapy study, make so much improvement over 2 years? All those with acute exacerbations were excluded from the study; all of the enrollees had long-standing low-back pain. Long-term follow-up was excellent and dropouts were few. Perhaps just putting a needle into someone's back is beneficial, independent of what, if anything, is injected. We should remember, of course, that every needle has a sharp end that goes into the patient and a blunt end that is attached to a health care provider. Anyone who thinks that all of the action occurs at the sharp end does not understand human behavior. Could regression to the mean be this potent a factor? Are there influences on the duration of symptoms that are not to be found within the patient's back? Do disability system and compensation factors have a time span that could have influenced the outcome of this study? Does anyone need costly and sometimes hazardous interventions for the treatment of nonspecific low-back pain? Could it have been that the IASP Back Pain in the Workplace project was correct about the absurdity of unproven interventions in nonspecific low-back pain?[1]

I hope that the authors continue to bring their intelligence to bear on the problem of low-back pain. Demedicalizing this common symptom, as proposed by Illich in 1983, might be an idea whose time has come. Separating the wheat from the chaff is long overdue in the arena of interventions for low back pain.

From the Department of Neurological Surgery, University of Washington, Seattle, Washington.
The manuscript submitted does not contain information about medical device(s)/drug(s).
No funds were received in support of this work. No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this manuscript.
Address correspondence to John D. Loeser, MD, Department of Neurological Surgery, University of Washington, Box 356470, Seattle, Washington 98195; E-mail: jdloeser@u.washington.edu

Reference

1. Fordyce WE. Back Pain in the Workplace. Seattle, IASP Press, 1995. In Illich I, ed. *Medical Nemesis: The Expropriation of Health*. New York: Pantheon Press; 1976.