Prolotherapy injections for chronic low-back pain

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Prolotherapy injections for chronic low-back pain [Review]

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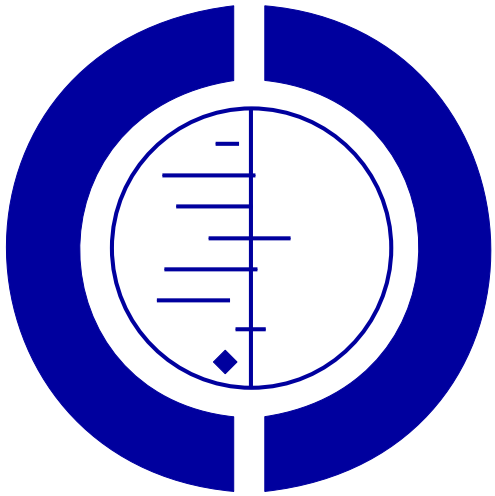

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ABSTRACT

Background
Prolotherapy is an injection-based treatment for chronic low-back pain. Proponents of prolotherapy suggest that some back pain stems from weakened or damaged ligaments. Repeatedly injecting them with irritant solutions is believed to strengthen the ligaments and reduce pain and disability. Prolotherapy protocols usually include co-interventions to enhance the effectiveness of the injections.

Objectives
To determine the efficacy of prolotherapy injections in adults with chronic low-back pain.

Search strategy
We searched CENTRAL (2004, issue 1), MEDLINE, EMBASE, CINAHL and Science Citation Index from their respective beginnings to January 2004, with no restrictions on language. We consulted content experts to ensure we had not missed any references.

Selection criteria
Randomised and quasi-randomised controlled trials comparing prolotherapy injections to control injections, either alone or in combination with other treatments, were included. Studies had to include measures of pain and disability before and after the intervention.

Data collection and analysis
Two authors independently selected the trials and assessed them for methodological quality. Treatment and control group protocols varied from study to study, making meta-analysis impossible.

Main results
We included four high quality studies with a total of 344 participants. All trials measured pain and disability levels at six months, three measured the proportion of participants reporting a greater than 50% reduction in pain or disability scores from baseline to six months.

Two studies showed significant differences between the treatment and control groups for those reporting over 50% reduction in pain or disability. Their results could not be pooled. In one, co-interventions confounded interpretation of results; in the other, there was no significant difference in mean pain and disability scores between the groups. In the third study, there was little or no difference between groups in the number of individuals who reported over 50% improvement in pain and disability. The fourth study reporting only mean pain and disability scores showed no differences between groups.

Authors' conclusions
There is conflicting evidence regarding the efficacy of prolotherapy injections in reducing pain and disability in patients with chronic low-back pain. Conclusions are confounded by clinical heterogeneity amongst studies and by the presence of co-interventions. There was no evidence that prolotherapy injections alone were more effective than control injections alone. However, in the presence of co-interventions, prolotherapy injections were more effective than control injections, more so when both injections and co-interventions were controlled concurrently.

PLAIN LANGUAGE SUMMARY

If used alone, prolotherapy injections do not have a role in the treatment of chronic low-back pain. When combined with other treatments, they may give prolonged partial relief of pain and disability.

Prolotherapy injections aim to reduce back pain by strengthening weakened ligaments. They are often combined with manipulation, exercises and injections into tender muscles. This review included four studies that examined the effect of prolotherapy injections on 344 patients with low-back pain that had lasted for longer than three months. Minor side effects from the treatment, such as increased back pain and stiffness, were common but short-lived.

BACKGROUND

Chronic low-back pain places an enormous burden on society, in terms of both patient suffering and cost (Quebec Task Force). This makes the search for more effective treatments a priority in research. Prolotherapy (also called sclerotherapy) is an injection-based treatment for chronic musculoskeletal pain. Its proposed mode of action is the reduction of joint instability through the strengthening of stretched or torn ligaments (Klein 1997). Its most common application in the back is chronic non-specific low-back pain that has not responded to other therapies. Protocols for prolotherapy for back pain in scientific studies to date vary, but all include the injection of an irritant (proliferant) solution into ligaments and tendinous attachments at weekly or fortnightly intervals for three to eight treatments. Protocols usually include one or more co-interventions that aim to enhance the effectiveness of treatment.

Proponents of prolotherapy believe that ligament injections trigger an influx of granulocytes, macrophages and fibroblasts, the release of growth factors and ultimately, collagen deposition. They hypothesise that this leads to strengthening of ligaments and a reduction in pain and disability. There are three major classes of proliferants commonly used in prolotherapy -- the irritants, the chemotactics and the osmotics (Banks 1991). There is some overlap in their purported actions. Irritants act by either damaging cells directly or by rendering the cells antigenic through alteration of surface proteins. Irritants include phenol, guaiacol and tannic acid. There is another category of irritants called particulates, exemplified by pumice flour. These act by triggering cellular trauma following injection into target tissues, and by directly attracting macrophages, which ingest them and secrete polypeptide growth factors. Chemotactics also act by attracting inflammatory cells. The only agent in this class is sodium morrhuate. The osmotic class of proliferants includes concentrated solutions of glucose, glycerin and zinc sulphate. They act by causing an osmotic shock to cells leading to the release of pro-inflammatory substances. Local anaesthetic (commonly lignocaine) is often added to proliferant solutions to reduce the pain of the irritant injections. An increase in mass and thickness in animal and human ligaments has been demonstrated in response to repeated injections of a commonly used solution containing glucose (dextrose), glycerine, phenol and lignocaine (lidocaine) (Klein 1989).

Prolotherapy injections are often supplemented by co-interventions (Ongley 1987; Dhillon 1997; Klein 1993; Yelland 2004). Prior to commencing prolotherapy injections, these may include, alone or in any combination, triamcinolone injections into hypersensitive tender points, infiltration of lumbosacral ligaments with lignocaine, or low-back manipulation under intravenous sedation and analgesia. During and after the course of prolotherapy injections, co-interventions may include, alone or in any combination, lumbar flexion and extension exercises to induce optimal strengthening of the treated ligaments, regular walking, encouragement to recommence previously painful activities and use of oral vitamin C, zinc and manganese supplements, ostensibly to facilitate collagen growth. Use of oral anti-inflammatory medications is discouraged during the treatment period as this may, in theory, suppress the inflammation triggered by the prolotherapy injections.

A randomised controlled trial of prolotherapy, comparing injections of this solution with saline controls (Ongley 1987) was included in a past Cochrane Review of injection therapies for low-back pain (Nelemans 2003). It was the only trial in this review that showed significant, sustained reductions in pain and disability at six months. However, the effect of the proliferant injections was unclear due to the concurrent comparison of co-interventions with sham co-interventions. This review did not include other trials of prolotherapy. Given this, and the overall lack of effective treatments for chronic low-back pain, we undertook this systematic review focusing on prolotherapy injections alone.

OBJECTIVES

The objective of this review is to determine the efficacy of prolotherapy injections in reducing pain and disability in chronic low-back pain in adults, aged 16 and older.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

We included all randomised controlled trials (RCT) and quasi-randomised controlled trials (using, for example, birth date, social security number, date in which participants enter study, etc to assign participants to groups) comparing prolotherapy injections to control injections or other therapies. We included trials with co-interventions that formed part of established prolotherapy protocols. Trials had to include measures of pain and disability before and after the intervention.

We excluded non-randomised controlled studies and non-controlled experimental studies such as case series or case-control studies. There were no limits on publication dates of trials or language of publication.

Types of participants

We selected studies that included participants aged 16 years and over, with a history of non-specific low-back pain of longer than three months duration. low-back pain was defined as pain in the lumbar region, with or without pain in the sacral region, gluteal regions and radiation to the lower extremities. Exclusion criteria in studies were lumbar/sacral radiculopathies and pathological causes of back pain, such as infection, neoplasm, metastasis, osteoporosis, rheumatoid arthritis, or fractures. The presence of participants with unresolved litigation or compensation claims was not a reason for exclusion.

Types of intervention

For inclusion, prolotherapy injections had to be administered to at least one group within the trial. Comparison groups could include injections with a control solution or a different therapy not involving injections. For chronic non-specific low-back pain, the prolotherapy solutions are injected into the ligaments and tendons regarded as the sources of the pain. The choice of injection sites is determined either by a standard list of points (Ongley 1987) or by the patterns of pain and tenderness (Dhillon 1997). The skin through which injections are given at each treatment visit is anaesthetised with wheals of local anaesthetic. The number of injection treatments ranges from three to eight and the interval between treatments ranges from one to two weeks (Ongley 1987; Dechow 1999; Dhillon 1997). Co-interventions used with prolotherapy injections vary with different protocols and are described in the background section above and the *Table of Characteristics of Included Studies.*

Types of outcome measures

The choice of outcomes for inclusion in this systematic review was based on those recommended by the editorial board of the Cochrane Back Review group (Deyo 1998). They included:

- low-back pain: Measures included visual analogue scale (Huskisson 1974) and the McGill Pain Questionnaire (Melzack 1987) or other validated quantitative measures. The mean (SD) pain scores and the proportion achieving more than 50% reduction in pain scores were used.
- low-back-related disability: Measures included the Oswestry disability questionnaire (Fairbank 1980), Roland-Morris disability scale(Roland 1983) (or its adaptations (Patrick 1995)) or other validated measures of disability. Both the mean (SD) disability and the proportion achieving more than 50% reduction in disability were used.
- overall improvement or satisfaction with treatment.
- well-being: measured by SF-12 (Ware 1996), SF-36 (Ware 1992), or EuroQoL (EuroQoL 1990).
- disability: measuring return to work, days of absenteeism, or days of reduced activities (Deyo 1998).
- physical examination: measuring range of motion, spinal flexibility, or muscle strength.
- side effects, medication use and health care use.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Back Group methods used in reviews.

Data sources
The following electronic databases were searched using the strategy outlined in the attached table (Table 01):

- The Cochrane Library Issue 1, 2004 (including the Cochrane Back Review group register, the Cochrane Central Register of Controlled Trials, the Physical Medicine and Rehabilitation Field and the Complementary Medicine Field trials register).
- MEDLINE (January 1966 to January 2004)
- EMBASE Rehabilitation and Physical Therapy field (January 1992 to January 2004)
- CINAHL (January 1982 to January 2004)
- Science Citation Index (January 1990 to January 2004) to search for additional reports of studies in relevant bibliographic references of all retrieved reports of RCTs and relevant reviews.

We sent content experts the list of studies identified from these databases to check it for completeness and to inform us of any missing studies. We included unpublished studies.

METHODS OF THE REVIEW

Selection of studies for inclusion

Two authors independently applied the inclusion criteria to the titles and abstracts of studies identified through aforementioned search strategies, to select studies for inclusion. There were no disagreements about the eligibility of studies for inclusion.

Assessment of methodological quality
The full text of all studies meeting inclusion criteria was obtained. The methodological quality of these studies was assessed independently by the two authors, neither of whom were co-authors of the studies. They were blinded to the studies' authors, institutional affiliation and journal. They rated each study according to the criteria list for methodological assessment and their methods of operationalisation recommended by the Cochrane Back Review group (van Tulder 2003) outlined below.

Criteria List for methodological quality assessment
The following criteria were scored as "Yes", "No" or "Don't know". The positive answers were summed, to obtain a score out of 11. Studies scoring six or more out of 11 were considered to be of high quality.

1. Was a method of randomisation performed?
2. Was the treatment allocation concealed?
3. Was the care provider blinded to the intervention?
4. Were co-interventions avoided or comparable?
5. Was the compliance acceptable in all groups?
6. Was the patient blinded to the intervention?
7. Was the outcome assessor blinded to the intervention?
8. Were the outcome measures relevant?
9. Was the withdrawal/drop-out rate described and acceptable?
10. Was the timing of the outcome assessment in both groups comparable?
11. Did the study include an intention-to-treat analysis?

The operationalisation of these criteria is outlined in an attached table (Table 02).

Data extraction
Data were extracted independently by the two authors using a data extraction form with sections on study design and setting, participant characteristics, interventions, outcomes, timing of outcomes and duration of effects, main results, withdrawals, adverse effects and conclusions.

Data analysis
For dichotomous outcome measures, the differences between groups in each study were expressed as the relative risk (RR) and risk difference (RD) with their respective 95% confidence intervals (95% CI). For between-group comparisons of continuous measures, the effect size was estimated as standardised mean differences with 95% CI to accommodate the different scales used in each study.

We evaluated clinical homogeneity by exploring the differences between the RCTs with regard to study population, types of interventions in treatment and control groups and the types of outcomes. We decided against analysis by statistical pooling because of the clinical heterogeneity amongst intervention groups and amongst control groups. No two studies tested the same component(s) of treatment and had the same number of injection treatments.

We described the results and conclusions using a rating system for levels of evidence recommended by the Cochrane Collaboration Back Review Group (van Tulder 2003). This consisted of four levels of scientific evidence, based on the quality and the outcome of the studies:

- Strong evidence - provided by generally consistent findings in multiple high quality RCTs.
- Moderate evidence - provided by generally consistent findings in one high quality RCT and one or more low quality RCTs, or by generally consistent findings in multiple low quality RCTs.
- Limited or conflicting evidence - only one RCT (either high or low quality) or inconsistent findings in multiple RCTs.
- No evidence - no RCTs.

DESCRIPTION OF STUDIES

See *Table of Characteristics of Included Studies* (Dechow 1999; Klein 1993; Ongley 1987; Yelland 2004)

METHODOLOGICAL QUALITY

All studies were of high quality, meeting at least nine of the 11 internal validity criteria set by the Cochrane Back Review Group (van Tulder 2003). A study by Ongley et al fulfilled all 11 criteria with the exception of the one regarding comparable co-interventions (Ongley 1987). This study was designed to concurrently compare four interventions (including prolotherapy injections) with four control interventions. Three of these, the initial lignocaine injections into ligaments, the manipulation following these injections, and the injection of muscle tender points with triamcinolone/lignocaine, were not blinded to the treating doctor, but the prolotherapy injections given by a different doctor were double-blinded. Klein et al fulfilled all 11 criteria (Klein 1993). Dechow et al fulfilled nine of the criteria as it was unclear if treatment allocation was concealed and whether the care provider was blinded to the type of injections given (Dechow 1999). The study by Yelland et al had a factorial design to test the efficacy of prolotherapy injections and exercises in the same study (Yelland 2004). It fulfilled all 11 criteria for the injections factor and nine of the criteria for the exercises factor, as the care provider was not blinded to the exercise status of participants.

RESULTS

The search strategy identified five studies, four of which were eligible for inclusion in the review (Ongley 1987; Klein 1993; Dechow 1999; Yelland 2004). The other study was a pilot comparative study with concurrent controls but was excluded as randomisation was not used (Yelland 2000). Contact with content experts revealed one further study submitted for publication (Wilkinson 2003). This study was excluded because 20% of its participants had thoracic or cervical spinal pain and the study design involved crossover between experimental and control injections on the second treatment, making long term results uninterpretable.

Study population

All studies included only adult patients whose pain had been present for over six months and had failed prior treatments. They all excluded patients with possible pathological causes of back pain, such as cancer, spondylolisthesis and radiculopathy, patients who had undergone surgery and those whose pain was the subject of unresolved worker's compensation or legal action.

Study design and interventions

The protocols for experimental and controls were complex and varied, making inter-trial comparisons difficult. They are outlined in the *Table of Characteristics of Included Studies*. No study had a control group that did not receive injections. Within each study, the experimental and control groups received the same protocol of ligament injections, but with different solutions. Ongley et al compared glucose/glycerine/phenol/lignocaine solution with a normal saline control solution (Ongley 1987). Klein et al (Klein 1993) and Dechow et al (Dechow 1999) compared glucose/glycerine/phenol/lignocaine solution with a lignocaine control solution, but Dechow et al differed markedly by having only three injection treatments compared with at least six treatments in all the other studies. Yelland et al compared a glucose/lignocaine solution with a saline solution, there being no phenol or glycerine components (Yelland 2004). This study also tested the effect of the exercise co-intervention using a factorial design, with independent random allocation of participants to either exercises or normal activity. This design allowed separate analysis of the attributable effects of the injections and the exercises. In contrast, Ongley et al tested several co-interventions with allocation tied to the injection group (Ongley 1987). The day before commencing the course of prolotherapy injections, the experimental group received initial triamcinolone/lignocaine injections into muscle tender points and high dose lignocaine injections into ligaments followed by manipulation, whereas control group had lignocaine-only injections into muscle tender points and then low dose lignocaine injections into ligaments followed by a sham manipulation. This design made it impossible to attribute any effect to a single component of the treatment protocol.

Study funding

Ongley et al (Ongley 1987) and Klein et al (Klein 1993) were funded by a combination of private research foundation grants and personal donations. Dechow et al (Dechow 1999) and Yelland et al (Yelland 2004) were funded by public research grants and Yelland et al had additional funding from private research foundation grants. No conflicts of interest were declared in any study.

Effect measurements

The primary outcomes in all studies were pain and disability. Pain was measured on a visual analogue scale in all studies and additionally by a McGill Pain Questionnaire in one study (Dechow 1999). Disability was measured by a Roland-Morris disability questionnaire or a modification thereof in three studies and by an Oswestry Disability Scale in one study (Dechow 1999). All studies reported mean scores for these outcomes at zero and six months. All studies, with the exception of Dechow et al (Dechow 1999), also reported the proportion achieving at least 50% reduction in pain and/or disability scores at six months. Several secondary outcomes, including physical performance testing and medication usage were reported, but not consistently across studies. Follow-up periods were six months, with the exception of Yelland et al that followed participants for twenty four months (Yelland 2004).

Efficacy

The key results for pain and disability are summarised in the *Table of Characteristics of Included Studies*, additional tables (Table 03; Table 04) and the analyses (see graphs). For between-group differences in the proportion of participants showing more than 50% reduction in scores from baseline at six months, two studies reported significant differences between the treatment group and the control group (Table 03). In Ongley et al, these proportions for disability were 88% and 39% respectively (RR 2.24, 95% CI 1.50 to 3.35, $p < 0.03$) (Ongley 1987). In Klein et al, these proportions for both pain and disability were 77% (treatment) and 53% (control) (RR 1.47, 95% CI 1.04 to 2.06, $p = 0.04$) (Klein 1993). In Yelland et al, these proportions were not significantly different. For pain they were 50% (treatment) and 46% (control) (RR 1.10, 95% CI 0.75 to 1.61, $p = 0.85$) and for disability they were 49% (treatment) and 32% (control)(RR 1.50, 95% CI 0.94 to 2.40, $p = 0.08$) (Yelland 2004). No such proportions were reported by Dechow et al (Dechow 1999).

The long term results in Yelland et al showed a similar pattern (Yelland 2004) (Table 03). At 12 months, the proportion of participants showing more than 50% reduction in scores from baseline for pain were 46% (treatment) and 36% (control) (RR 1.29, 95% CI 0.81 to 2.04, $p = 0.32$) and for disability were 42% (treatment) and 32% (control) (RR 1.31, 95% CI 0.79 to 2.16, $p = 0.32$). At 24 months, the proportion of participants showing more than 50% reduction in scores from baseline for pain were 48% (treatment) and 39% (control) (RR 1.22, 95% CI 0.75 to 1.97, $p = 0.52$) and for disability were 48% (treatment) and 35% (control) (RR 1.37, 95% CI 0.82 to 2.27, $p = 0.28$).

For between group differences in the mean pain and disability scores at six months, the only study that reported significantly greater reductions in mean pain and disability scores favouring the treatment group was that by Ongley et al (Ongley 1987) (Table 04). For pain scores, the SMD was -1.00 (95% CI -1.46 to -0.53, p < 0.001) and for disability, the SMD was -0.81 (95% CI -1.26 to -0.35, p < 0.001). In Klein et al, the difference in these reductions favouring the treatment group was reported as borderline significant (Klein 1993). For pain scores, the SMD was -0.31 (95% CI -0.76 to 0.13, p = 0.056) and for disability, the SMD was -0.09 (95% CI -0.53 to 0.35, p = 0.068). Only with exclusion of a subgroup of participants with hypersensitive gluteal tender points, treated with triamcinolone injections on the first day of treatment, did the difference in these reductions achieve statistical significance (p = 0.030 for mean pain and p = 0.016 for mean disability). In Dechow et al, there were no significant differences between groups (Dechow 1999). For pain scores, the SMD was 0.14 (95% CI -0.32 to 0.59, p not reported) and for disability, the SMD was 0.03 (95% CI -0.43 to 0.49, p not reported). Similarly, in Yelland et al, there were no significant differences between groups (Yelland 2004). For pain scores, the SMD was -0.10 (95% CI -0.47 to 0.28, p = 0.61) and for disability, the SMD was -0.22 (95% CI -0.59 to 0.16, p = 0.30). Similarly, there were no significant differences between groups in this study at 12 and 24 months.

Changes in secondary outcomes reflected those observed in the primary outcomes with a few notable exceptions. In Ongley et al, there were no differences between groups in clinical signs at six months (Ongley 1987). The improvement in pain diagram grid scores at six months in Klein et al was significantly better in the treatment group than in the control group (P = 0.025) (Klein 1993), but not in the other studies. Significant improvements from baseline occurred in lumbar motion range, isometric strength and velocity of movement in treatment and control groups in Klein et al, but there were no significant differences between groups (Klein 1993).

A separate analysis of the exercise co-intervention in Yelland et al reported no differences in pain and disability responses between exercise and normal activity groups at any point in the study (Yelland 2004).

Adverse events

By far, the commonest adverse events reported were temporary increases in back pain and stiffness following injections, reported by nearly all participants at some point in three studies (Ongley 1987; Klein 1993; Yelland 2004), with only a few reporting increased pain post-injection in the remaining study (Dechow 1999). Post-injection headaches suggestive of lumbar puncture occurred in two per cent in Klein et al (Klein 1993) and in four per cent in Yelland et al (Yelland 2004). In Ongley et al, there was also a two per cent incidence of postmenopausal spotting, attributed to the initial triamcinolone injections (Ongley 1987). In Yelland et al, four participants (4%) developed leg pain with neurological features, but CT or MRI scanning showed evidence of nerve root compression by herniated discs and/or osteophytes (Yelland 2004). Three of these resolved with symptomatic treatment and the fourth with a laminectomy. In Yelland et al, there were also reports of nausea/diarrhoea in 42%, thoracic spinal pain in 10%, and other symptoms in 56%, but symptoms were generally transient. No study reported any significant differences in the incidence of adverse events between treatment and control groups.

DISCUSSION

Study Selection

Despite an extensive search, only four articles on prolotherapy injections for chronic low-back pain were available for review. The treatment and control group protocols varied from study to study, making meta-analysis impossible. Consequently, the conclusions of this review are based on the results of individual studies.

Methodological Quality

The quality of studies was high, with all studies rating nine points or greater on an 11 point assessment of internal validity. Ongley et al, Klein et al and Yelland et al all met the important criteria of allocation concealment and blinding of the treating doctor to the composition of the injection solution (Ongley 1987; Klein 1993; Yelland 2004). It was unclear whether Dechow et al met these criteria (Dechow 1999). Outcome assessment was blinded in all studies, but as the primary outcomes were self-assessed pain and disability, this criterion is less important than in studies where primary outcomes are measured objectively by an assessor.

Efficacy of Prolotherapy Injections

There is conflicting evidence regarding the efficacy of prolotherapy injections for the treatment of chronic low-back pain. Conclusions are confounded by clinical heterogeneity amongst studies and by the presence of co-interventions. Two studies that compared prolotherapy injections directly against control injections found no evidence that prolotherapy injections are more effective (Dechow 1999; Yelland 2004). One study comparing prolotherapy injections with control injections, in the presence of the same co-interventions, found prolotherapy injections to be more effective for the proportion achieving more than 50% reduction in pain or disability (Klein 1993), but not for mean pain or disability scores. The remaining study demonstrated that prolotherapy injections with co-interventions are more effective than control injections with control co-interventions (Ongley 1987). However, this study failed to define the contribution of the prolotherapy injections to the effectiveness of treatment. Further research will be necessary to reconcile these conflicting findings.

The confounding effect of co-interventions raises important questions about the active component(s) of treatment in prolotherapy protocols. Of note were the significant and sustained reductions

in pain and disability in both the intervention and control groups of studies with six or more injection treatments with at least 20 ml of solution, in contrast with the lack of response in the study with three injection treatments with 10 ml of solution. This raises the question of a dose-response phenomenon with injections in the treatment of chronic low-back pain. However, in the absence of a study with randomisation to different doses of treatment, it would be improper to extrapolate a dose-response phenomenon for injections. An alternative explanation of this phenomenon is that a non-specific effect of increased contact with a confident and caring practitioner led to the improvement.

In all studies, part of the response, in both treatment and control groups, may be attributed to 'regression to the mean' and/or the natural history of the back complaint. The phenomenon of 'regression to the mean' results from an increased motivation by people to join trials when their problem is at its worst, making spontaneous improvement more likely. The natural history of low-back pain that is as long-standing as that described in the included studies is unclear, although evidence from a longitudinal study suggests that the longer the back pain is consistently reported, the more likely it is to persist (Smedley 1998). The mean duration of pain in the three studies (Ongley 1987; Klein 1993; Yelland 2004) showing sustained improvement in both treatment and control groups exceeded eight years, making it difficult to attribute much of the observed improvement to natural history.

These three studies were also the studies with multiple co-interventions. Co-interventions variously included an initial infiltration of ligaments with local anaesthetic followed by manipulation under sedation, superficial skin injections of local anaesthetic, the injection of gluteal tender points with triamcinolone/lignocaine, encouragement to perform previously painful activities (activation), vitamin and mineral supplements and flexion/extension exercises. One study specifically examined the effect of the flexion/extension exercises (Yelland 2004) and found they were no more effective than normal activity. The study by Ongley et al (Ongley 1987), the only one to show a clear difference between treatment and control groups, has been construed in another review as evidence of the efficacy of manipulation (van Tulder 1997). However, it fails to support the efficacy of manipulation just as it fails to support the efficacy of prolotherapy injections, because the intervention group differed from the control group in four respects - the pre-manipulation injections, the manipulation, the muscle tender point injections and the prolotherapy injections.

An assessment of the effects of the glucose/glycerine/phenol/lignocaine protocol used by Ongley et al was confounded by the presence of co-interventions (Ongley 1987). In response to the criticism of the design of this study, Klein et al made the glucose/glycerine/phenol components of the proliferant solution the only variable between treatment and control groups (Klein 1993). In this study, which involved six injection treatments, the prolotherapy group had a statistically significant advantage over the control group in the proportion of participants showing more than 50% reduction in scores from baseline to six months. However, there were no statistically significant differences between the groups in mean pain and disability scores unless those with hyperirritable gluteal tender points were excluded from the analysis. In their discussion, Klein et al considered a gradual denervating effect of the phenol component as a possible mechanism of pain relief. However, the study by Dechow et al, which used the same components of the injection solution (but with only three injection treatments), showed no such response and no significant differences between groups (Dechow 1999). Yelland et al evaluated the effects of glucose/lignocaine injections and found they resulted in no greater improvement than saline injections (Yelland 2004). However, both the prolotherapy and control groups in this study demonstrated significant and sustained reductions in pain and disability scores over a two-year period.

Collectively, these findings leave many questions unanswered about the efficacy and mechanism of action of prolotherapy injections. Klein et al considered a gradual denervating effect of the phenol component as a possible mechanism of pain relief (Klein 1993). Alternatively, the beneficial effect could be attributed to the needles rather than the specific injection solution, by a counter-irritation effect. This has been shown elsewhere to inhibit pain in humans (Reinert 2000). Finally, the original hypothesis that reductions in pain and disability stem from strengthening of ligaments by prolotherapy injections has neither been confirmed nor refuted by the evidence provided by the four studies.

Prolotherapy injections are not without adverse events, with the majority of participants experiencing a transient increase in pain and stiffness and a few percent with severe headaches suggestive of lumbar puncture. However, no serious or permanent adverse events were reported. Patients considering prolotherapy for their back pain need to balance this adverse event profile against the possible benefits it may offer. Patients considering prolotherapy should balance the possibility of transient adverse events against the potential benefits of this therapy.

AUTHORS' CONCLUSIONS

Implications for practice

Given the present studies, prolotherapy injections alone do not have evidence of a role in the treatment of chronic low-back pain. However, repeated ligament injections, irrespective of the solution used, may give prolonged partial relief of pain and disability as part of a multimodal treatment programme. Transient increases in pain and stiffness are likely with such treatment, but serious adverse events are unlikely.

Implications for research

Further experimental and clinical studies are needed to elucidate the effects of prolotherapy injections. These studies should also in-

vestigate the specific effects of the most common co-interventions to prolotherapy injections, such as superficial and deep injections of local anaesthetic, manipulation and vitamin/mineral supplements. Further research is needed into the predictors of treatment success, so that it can be better targeted to those who may benefit from it.

Apart from one non-randomised pilot study (Yelland 2000), no studies have compared prolotherapy with non-injection therapies. There is a need for RCTs in this area. There is also a need for RCTs on prolotherapy for discogenic back pain confirmed by discography, following promising results from a pilot study of this treatment (Klein 2003).

POTENTIAL CONFLICT OF INTEREST

The lead author (MY) is an author of one of the studies included in this review. He was not involved in the assessment of his trial for this review. One consumer representative (PV) was a participant in this trial, giving him personal experience in the application of prolotherapy for chronic low-back pain. The second consumer representative (MS) is a consumer representative for the Back Review Group.

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REFERENCES

References to studies included in this review

Dechow 1999 *{published data only}*
Dechow E, Davies RK, Carr AJ, Thompson PW. A randomized, double-blind, placebo-controlled trial of sclerosing injections in patients with chronic low back pain. *Rheumatology* 1999;**38**:1255–1259.

Klein 1993 *{published data only}*
Klein RG, Eek BC, DeLong WB, Mooney V. A randomized double-blind trial of dextrose-glycerine-phenol injections for chronic low back pain. *Journal of Spinal Disorders* 1993;**6**(1):23–33.

Ongley 1987 *{published data only}*
Ongley MJ, Klein RG, Dorman TA, Eek BC, Hubert LJ. A new approach to the management of low back pain. *Lancet* 1987;**2**(8551): 143–146.

Yelland 2004 *{published data only}*
Yelland MJ, Glasziou PP, Bogduk N, Schluter PJ, McKernon M. Prolotherapy injections, saline injections and exercises for chronic low back pain: a randomised trial. *Spine* 2004;**29**(1):9–16.

References to studies excluded from this review

Wilkinson 2003
Wilkinson HA. A single-blinded randomized and crossover study of phenolic prolotherapy for periosteal trigger points causing axial spinal pain. Unpublished.

Yelland 2000
* Yelland M, Yeo M, Schluter P. Prolotherapy injections for chronic low back pain - results of a pilot comparative study. *Australasian Musculoskeletal Medicine* 2000;**5**(2):20–23.

Additional references

Banks 1991
Banks AR. A rational for prolotherapy. *Journal of Orthopaedic Medicine* 1991;**13**(3):54–9.

Deyo 1998
Deyo RA, Battie M, Beurskens AJHM, Bombardier C, Croft P, Koes B, et al. Outcome measures for low back pain research - a proposal for standardized use. *Spine* 1998;**23**(18):2003–13.

Dhillon 1997
Dhillon GS. Prolotherapy in lumbo-pelvic pain. *Australasian Musculoskeletal Medicine* 1997;**2**(2):17–9.

EuroQoL 1990
EuroQoL Group. EuroQoL: A new facility for the measurement of health-related quality-of-life. *Health Policy* 1990;**16**:199–208.

Fairbank 1980
Fairbank JCT, Davies JB, Mbaot JC, O'Brien JT. The Oswestry Low Back Pain Disability Questionnaire. *Physiotherapy* 1980;**66**:271–3.

Huskisson 1974
Huskisson EC. Measurement of pain. *Lancet* 1974;**2**:1127–31.

Jensen 1989
Jensen ME, Karoly P, O'Riordan EF, Bland Jr F, Burns RS. A subjective experience of acute pain. An assessment of the utility index of 10 indices. *Clin J Pain* 1989;**5**(2):153–9.

Klein 1989
Klein RG, Dorman TA, Johnson CE. Proliferant injections for low back pain: histologic changes of injected ligaments and objective measurements of spinal mobility before and after treatment. *The*

Journal of Neurological & Orthopaedic Medicine & Surgery 1989;**10** (2):123–6.

Klein 1997
Klein RG, Eek BCJ. Prolotherapy: An alternative approach to managing low back pain. *The Journal of Musculoskeletal Medicine* 1997; **14**(5):45–59.

Klein 2003
Klein RG, Eek BCJ, O'Neill CW, Elin C, Mooney V, Derby RR. Biochemical injection treatment for discogenic low back pain. *The Spine Journal* 2003;**3**:220–226.

Melzack 1987
Melzack R. The short-form McGill Pain Questionnaire. 1987;**Pain** (32):191–7.

Nelemans 2003
Nelemans PJ, de Bie RA, de Vet HCW, Sturmans F. Injection therapy for subacute and chronic benign low back pain (Cochrane Review). In: *The Cochrane Library*, 4, 2003. Chichester, UK: John Wiley & Sons, Ltd CD001824.

Patrick 1995
Patrick DL, Deyo RA, Atlas SJ, Singer DE, Chapin A, Keller RB. Assessing health-related quality-of -life in patients with sciatica. *Spine* 1995;**20**:1899–1909.

Quebec Task Force
Quebec Task Force on Spinal Disorders. Scientific approach to the assessment and management of activity related spinal disorders: a monograph for clinicians. *Spine* 1987;**12**(Supp):S1–59.

Reinert 2000
Reinert A, Treede R, Bromm B. The pain inhibiting pain effect: an electrophysiological study in humans. *Brain Research* 2000;**862**(1-2): 103–10.

Roland 1983
Roland M, Morris R. A study of the natural history of back pain. I: Development of a reliable and sensitive measure of disability in low back pain. *Spine* 1983;**8**:141–4.

Smedley 1998
Smedley J, Inskip H, Cooper C, Coggon D. Natural history of low back pain. A longitudinal study in nurses. *Spine* 1998;**23**(22):2422–6.

van Tulder 1997
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**(18):2128–56.

van Tulder 2003
van Tulder M, Furlan A, Bombardier C, Bouter L. Updated method guidelines for systematic reviews in the Cochrane Collaboration Back Review Group. *Spine* 2003;**28**(12):1290–9.

Ware 1992
Ware JE, Sherbourne C. The MOS 36-item short-form Survey (SF-36): I. Concept framework and item selection. *Med Care* 1992; **30**:473–83.

Ware 1996
Ware JE, Kosinski M, Keller SD. A 12-item short form health survey. *Med Care* 1996;**34**:220–3.

* *Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	**Dechow 1999**
Methods	Randomized allocation by random number list. Double blind (participants and observers).
Participants	Departments of Rheumatology and Orthopaedic Surgery, East Dorset. 74 patients with chronic non-specific back pain, duration over 6 months. Experimental: mean age (SD) 46 (11), 20 males, median duration of pain >10 years, past compensation 17%, past back surgery 11%. Control group: mean age (SD) 46 (11), 20 males, median duration of pain >10 years, past compensation 5%, past back surgery 11%
Interventions	Experimental group (E) (n = 36): Weekly injections of lumbopelvic ligaments with glucose (12.5%) glycerine (12.5%) phenol (1.2%) 0.25% lignocaine, 10 ml in total. 3 injection treatments. Control group (C) (n = 38): Weekly injections of lumbopelvic ligaments with 0.5% lignocaine, 10 ml in total. 3 injection treatments.
Outcomes	Mean (SD) of outcomes at baseline and at 1, 3 and 6 months after intervention: VAS pain - (E) 5.3 (5.4), 5.2 (4.8), 5.1 (4.8), 5.2 (5.4); (C) 5.3 (5.5), 4.8 (4.6), 5.3 (5.2), 4.4 (6.2).

	Oswestry disability scale - (E) 34 (36), 34 (36), 36 (36), 36 (30); (C) 33 (37), 33 (37), 34 (37), 35 (37).
Notes	Methodological quality score 9/11. Allocation concealment unclear; Treating doctor not blinded to injection type.
Allocation concealment	B

Study	**Klein 1993**
Methods	Randomized allocation by random numbers table. Double blind (participants and observers).
Participants	Sansum Medical Clinic, Santa Barbara, California 80 participants with chronic non-specific low back pain, duration over 6 months. Experimental: mean age (SD) 44.6 (8.6), 21 males, years of pain (SD) 11.2 (7.9). Control group: mean age (SD) 43.5 (9.2), 20 males, years of pain (SD) 11.8 (10.1).
Interventions	Experimental group (E) (n = 39): Weekly injections of lumbopelvic ligaments with glucose (12.5%) glycerine (12.5%) phenol (1.25%) 0.25% lignocaine, up to 30 ml in total. 6 injection treatments. Control group (C) (n = 40): Weekly injections of lumbopelvic ligaments with 0.25% lignocaine, up to 30 ml in total. 6 injection treatments. Both groups: Initial injection of lumbopelvic ligaments with 0.5% lignocaine followed by forceful manipulation and injection of gluteal tender points (if present) with triamcinolone/lignocaine; 200 flexion/extension exercises daily and 1 mile walk 5 times per week
Outcomes	Mean (SD) of outcomes at baseline and at 6 months after intervention 1. VAS pain: (E) 4.88 (1.30), 2.29 (1.67); (C) 4.56 (1.12), 2.85 (1.88) 2. Roland disability questionnaire added with 9 questions from Waddell's chronic disability index: (E) 9.36 (3.56), 4.04 (3.71) (C) 8.25 (3.26), 4.38 (4.05).
Notes	Methodological quality score 11/11
Allocation concealment	A

Study	**Ongley 1987**
Methods	Randomized allocation by random numbers table. Double blind (participants and observers).
Participants	Sansum Medical Clinic, Santa Barbara, California 81 participants with chronic non-specific low back pain, duration over 1 year. Experimental: mean age (range) 45 (23-70), 18 males, years of pain (range) 8.98 (1-30), 12 with radiation of pain into legs. Control group: mean age (range) 43 (23-70), 20 males, years of pain (range) 10.72 (1-35), 12 with radiation of pain into legs.
Interventions	Experimental group (E) (n = 40): Injection of lumbopelvic ligaments with 60 mls of 0.5% lignocaine followed by forceful manipulation and injection of gluteal tender points with triamcinolone/lignocaine. Then weekly injections of lumbopelvic ligaments with glucose (12.5%) glycerine (12.5%) phenol (1.25%) 0.25% lignocaine, 20 ml in total. 6 injection treatments. Controls (C) (n = 41): Injection of lumbopelvic ligaments with 10 mls of 0.5% lignocaine followed by non-forceful manipulation and injection of gluteal tender points with lignocaine. Then weekly injections of lumbopelvic ligaments with 0.9% saline, 20 ml in total. 6 injection treatments. Both groups: Encouraged to do previously painful activities and 150 flexion exercises daily.
Outcomes	Mean (SD) of outcomes at baseline and at 1, 3 and 6 months after intervention

Characteristics of included studies (*Continued*)

	1. VAS pain: (E) 3.78 (1.20), 2.13 (1.39), 1.77 (1.39), 1.50 (1.34); (C) 3.99 (1.22), 3.06 (1.86), 2.93 (1.60), 3.08 (1.77). 2. Roland disability questionnaire added with 9 questions from Waddell's chronic disability index: (E) 11.45 (5.25, 4.00 (3.90), 4.70 (4.62), 3.43 (4.61); (C) 11.82 (5.31); 8.37 (6.66), 8.49 (6.66), 8.29 (7.04)
Notes	Methodological quality score 10/11. Co-interventions not comparable.
Allocation concealment	A

Study	**Yelland 2004**
Methods	Randomized allocation by random numbers table. Double blind (participants and observers).
Participants	Inala Health Centre General Practice, Brisbane, Australia 110 participants with chronic non-specific low back pain, duration over 6 months. Experimental: mean age (SD) 51.5 (10.6), 32 males, years of pain (SD) 14.8 (10.9), 24 with radiation of pain into legs. Control group: mean age (SD) 49.4 (10.4), 31 males, years of pain (SD) 13.8 (9.3), 23 with radiation of pain into legs.
Interventions	Experimental group (E) (n = 54): Fortnightly injections of lumbopelvic ligaments with glucose (20%) and lignocaine (0.2%), 10 to 30 mls, mean number of injection treatments 7 Control group (C) (n = 56): Fortnightly injections of lumbopelvic ligaments with saline (0.9%), 10 to 30 mls, mean number of injection treatments 7 Both groups: Superficial injections of lignocaine over deep injection points; oral vitamin C, zinc and manganese supplements daily. Randomly assigned to 40 flexion/extension exercises daily, experimental (n = 28), control (n = 27), or normal activity, experimental (n = 26), control (n = 29) .
Outcomes	Mean (SD) of outcomes at baseline and 6, 12 and 24 months after commencing intervention. 1. VAS pain: (E) 51.9 (19.3), 31.4 (26.6), 33.1 (24.5), 32.8 (25.8); (C) 55.0 (20.7), 34.0 (27.5), 36.6 (27.9), 37.1 (24.6).
Notes	Methodological quality score 11/11
Allocation concealment	A

Characteristics of excluded studies

Wilkinson 2003	20% of its participants had thoracic or cervical spinal pain and were not analysed separately. Study design involved crossover between experimental injections of bupivicaine/phenol/glycol and control injections of bupivicaine on the second treatment, making long term results uninterpretable.
Yelland 2000	A multi-centre pilot study comparing the effectiveness of prolotherapy with a range of other conservative treatments for the treatment of chronic low back pain. Excluded as randomisation was not used.

ADDITIONAL TABLES

Table 01. Search strategy

The MEDLINE Silverplatter database was searched using the following strategy:
#1 PROLOTHERAPY (in the text)
#2 SCLEROTHERAPY (MeSH term, all subheadings included)
#3 SCLEROTHERAPY (in the text)

Table 01. Search strategy (*Continued*)

#4 DEXTROSE or GLUCOSE or GLYCERINE or PHENOL or MORRHUATE or GUAIAICOL or TANNIC ACID or PUMICE or ZINC or PROLIFERANT
#5 BACK PAIN (MeSH term, all subheadings included)
#6 BACK PAIN (in the text)
#7 #1 or #2 or #3 or #4 and (#5 or #6)
#8 RANDOMIZED-CONTROLLED-TRIALS (in publication type)
#9 CONTROLLED-CLINICAL-TRIALS in (in publication type)
#10 RANDOMISED CONTROLLED TRIALS (in the text)
#11 random-allocation (MeSH term, all subheadings included)
#12 double-blind-method (MeSH term, all subheadings included)
#13 single-blind method (MeSH term, all subheadings included)
#14 #8 or #9 or #10 or #11 or #12 or #13
#15 #7 and #14
The Cochrane Library was searched using lines #1 to #7 of the above strategy. EMBASE was searched using the strategy recommended by the Cochrane Back Review group (van Tulder 2003). CINAHL was searched using the same terms used in the MEDLINE Silverplatter search.

Table 02. Operalisation of criteria list for methodological quality assessment

1. A random (unpredictable) assignment sequence. Methods of allocation using date of birth, date of admission, hospital numbers, or alternation should not be regarded as appropriate.
2. Assignment generated by an independent person not responsible for determining the eligibility of the patients. This person has no information about the persons included in the trial and has no influence on the assignment sequence or on the decision about eligibility of the patient
3 The reviewer determines when enough information about the blinding of the care provider is given in order to score a "yes."
4. Co-interventions should either be avoided in the trial design or comparable between the index and control groups.
5. The reviewer determines when the compliance to the interventions is acceptable, based on the reported intensity, duration, number and frequency of sessions for both the index intervention and control intervention(s)
6. The reviewer determines when enough information about the blinding of the patient is given in order to score a "yes".
7. The reviewer determines (per outcome parameter) when enough information about blinding is given in order to score a "yes."
8. The reviewer determines whether the outcome measures were relevant. For back pain, we recommend considering pain, a global measure of improvement, back specific functional status, generic functional status, and return-to-work to be relevant
9. Participants included in the study but who did not complete the observation period or were not included in the analysis must be described. If the percentage of withdrawals and drop-outs does not exceed 20% for short-term follow-up and 30% for long-term follow˜up and does not lead to substantial bias, a "yes" is scored. (N.B., these percentages are arbitrary, not supported by literature).
10. Timing of outcome assessment should be identical for all intervention groups and for all important outcome assessments.
11. All randomized patients are reported/analyzed for the most important moments of effect measurement (minus missing values) irrespective of non compliance and co-interventions.

Table 03. Between-group differences:no. participants with >50% reduction in pain/disabilit

Study	Time from baseline	Outcome variable	Relative risk(95%CI)	P-value	Risk difference(95%C
Ongley 1987	6 months	Disability	2.24 (1.50, 3.35)	<0.03	0.48 (0.38, 0.67)
Klein 1993	6 months	Pain or disability	1.47 (1.04, 2.06)	0.04	0.24 (0.04, 0.45)
Yelland 2004	6 months	Pain	1.10 (0.75, 1.61)	0.85	0.05 (-0.14, 0.23)
Yelland 2004	6 months	Disability	1.50 (0.94, 2.40)	0.08	0.16 (-0.02, 0.34)

Table 03. Between-group differences:no. participants with >50% reduction in pain/disabilit (*Continued*)

Study	Time from baseline	Outcome variable	Relative risk(95%CI)	P-value	Risk difference(95%C
Yelland 2004	12 months	Pain	1.29 (0.81, 2.04)	0.32	0.10 (-0.08, 0.29)
Yelland 2004	12 months	Disability	1.31 (0.79, 2.16)	0.32	0.10 (-0.08, 0.28)
Yelland 2004	24 months	Pain	1.22 (0.75, 1.97)	0.39	0.08 (-0.12, 0.29)
Yelland 2004	24 months	Disability	1.37 (0.82, 2.27)	0.28	0.13 (-0.08, 0.33)

Table 04. Between-group differences for mean levels of pain and disability

Study	Time from baseline	Outcome variable	SMD (95% CI)
Ongley 1987	6 months	Pain	-1.00 (-1.46 to -0.53)
Ongley 1987	6 months	Disability	-0.81 (-1.26 to -0.35)
Klein 1993	6 months	Pain	-0.31 (-0.76 to 0.13)
Klein 1993	6 months	Disability	-0.09 (-0.53 to 0.35)
Dechow 1999	6 months	Pain	0.14 (-0.32 to 0.59)
Dechow 1999	6 months	Disability	0.03 (-0.43 to 0.49)
Yelland 2004	6 months	Pain	-0.10 (-0.47 to 0.28)
Yelland 2004	6 months	Disability	-0.22 (-0.59 to 0.16)
Yelland 2004	12 months	Pain	-0.13 (-0.51 to 0.25)
Yelland 2004	12 months	Disability	-0.28 (-0.67 to 0.10)
Yelland 2004	24 months	Pain	-0.17 (-0.59 to 0.25)
Yelland 2004	24 months	Disability	-0.13 (-0.55 to 0.29)

ANALYSES

Comparison 01. Dichotomous pain data at 6 months

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 >50% reduction in pain at 6 months			Relative Risk (Fixed) 95% CI	Totals not selected

Comparison 02. Dichotomous disability data at 6 months

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 >50% reduction in disability at 6 months			Relative Risk (Fixed) 95% CI	Totals not selected

Comparison 03. Continuous pain data at 6 months

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 VAS pain at 6 months			Standardised Mean Difference (Fixed) 95% CI	Totals not selected

Comparison 04. Continuous disability data at 6 months

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Disability score at 6 months			Standardised Mean Difference (Fixed) 95% CI	Totals not selected

INDEX TERMS

Medical Subject Headings (MeSH)

Chronic Disease; Combined Modality Therapy; Exercise Therapy; Glucose [administration & dosage]; Glycerol [administration & dosage]; Injections [adverse effects; *methods]; Irritants [administration & dosage]; Lidocaine [administration & dosage]; Ligaments [*drug effects]; Low Back Pain [*drug therapy]; Phenol [administration & dosage]; Randomized Controlled Trials

MeSH check words

Humans

COVER SHEET

Title	Prolotherapy injections for chronic low-back pain
Authors	Yelland MJ, Del Mar C, Pirozzo S, Schoene ML, Vercoe P
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GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Dichotomous pain data at 6 months, Outcome 01 >50% reduction in pain at 6 months

Review: Prolotherapy injections for chronic low-back pain

Comparison: 01 Dichotomous pain data at 6 months

Outcome: 01 >50% reduction in pain at 6 months

Study	Prolotherapy n/N	Control n/N	Relative Risk (Fixed) 95% CI	Relative Risk (Fixed) 95% CI
Klein 1993	30/39	21/40		1.47 [1.04, 2.06]
Yelland 2004	27/53	26/56		1.10 [0.75, 1.61]

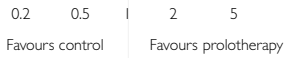
Analysis 02.01. Comparison 02 Dichotomous disability data at 6 months, Outcome 01 >50% reduction in disability at 6 months

Review: Prolotherapy injections for chronic low-back pain

Comparison: 02 Dichotomous disability data at 6 months

Outcome: 01 >50% reduction in disability at 6 months

Study	Prolotherapy n/N	Control n/N	Relative Risk (Fixed) 95% CI	Relative Risk (Fixed) 95% CI
Klein 1993	30/39	21/40		1.47 [1.04, 2.06]
Ongley 1987	35/40	16/41		2.24 [1.50, 3.35]
Yelland 2004	26/54	18/56		1.50 [0.94, 2.40]



Analysis 03.01. Comparison 03 Continuous pain data at 6 months, Outcome 01 VAS pain at 6 months

Review: Prolotherapy injections for chronic low-back pain

Comparison: 03 Continuous pain data at 6 months

Outcome: 01 VAS pain at 6 months

Study	Prolotherapy N	Prolotherapy Mean(SD)	Control N	Control Mean(SD)	Standardised Mean Difference (Fixed) 95% CI	Standardised Mean Difference (Fixed) 95% CI
Dechow 1999	36	5.20 (5.40)	38	4.40 (6.20)		0.14 [-0.32, 0.59]
Klein 1993	39	2.29 (1.67)	40	2.85 (1.88)		-0.31 [-0.76, 0.13]
Ongley 1987	40	1.50 (1.34)	41	3.08 (1.77)		-1.00 [-1.46, -0.53]
Yelland 2004	53	31.40 (26.60)	56	34.00 (27.50)		-0.10 [-0.47, 0.28]

Analysis 04.01. Comparison 04 Continuous disability data at 6 months, Outcome 01 Disability score at 6 months

Review: Prolotherapy injections for chronic low-back pain

Comparison: 04 Continuous disability data at 6 months

Outcome: 01 Disability score at 6 months

Study	Treatment		Control		Standardised Mean Difference (Fixed)	Standardised Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	95% CI
Dechow 1999	36	35.00 (30.00)	38	34.00 (36.00)		0.03 [-0.43, 0.49]
Klein 1993	39	4.04 (3.71)	40	4.38 (4.05)		-0.09 [-0.53, 0.35]
Ongley 1987	40	3.43 (4.61)	41	8.29 (7.04)		-0.81 [-1.26, -0.35]
Yelland 2004	53	7.90 (7.12)	56	9.30 (5.73)		-0.22 [-0.59, 0.16]