

**Dagenais S, Yelland MJ, et al. Prolotherapy injections for chronic low back pain (Review). Cochrane Database of Systematic Reviews 2007, Issue 2, Art# CD004059.**

Design: Systematic reviews of controlled clinical trials

PICOS:

- Patient population: Adults over 18 with a history of non-specific low back pain lasting more than 3 months, defined as pain in the lumbar region, with or without pain in the sacrum, gluteal region, or lower extremity
  - o Exclusion criteria were radiculopathies and pain due to pathologies such as infection, neoplasm, metastasis, osteoporosis, rheumatoid arthritis, or fractures
- Interventions: Administration of any form of prolotherapy to at least one group in the study
- Comparison: Injection of a control solution or treatment not involving any injection
  - o Prolotherapy was injected into the ligaments and tendons which are regarded as pain generators
  - o Injection sites could be determined either by a predetermined list of points or by the pattern of pain and tenderness specific to the patient
  - o Number of injections ranged from 3 to 8 with an interval of 1 or 2 weeks between injections
  - o Co-interventions varied between studies and were not specified for study selections
- Outcomes: Low back pain, low back disability, general/overall improvement or satisfaction with treatment, well-being measured by SF-12, return to work, physical examination findings, medication/health care use
- Study types: Randomized and quasi-randomized controlled trials
  - o Non-controlled studies and case series were excluded

Study selection:

- Databases included MEDLINE, EMBASE, CINAHL, AMED, and the Cochrane Central Register of Controlled Trials through October 2006
- Two authors independently applied inclusion criteria to articles retrieved through search strategies; no disagreements between authors occurred during the selection process
- Quality was assessed using the Cochrane Back Review group criteria (randomization, allocation concealment, blinding, co-interventions, etc)
- The authors decided against pooling study results because of heterogeneity of intervention and control groups
- Literature was updated in July 2009 without addition of new studies

Results:

- Five studies were eligible for inclusion in the review; four were considered high quality in terms of internal validity (control of bias) of the Cochrane Back Review group
- In each study, the control group had an injection of some description, but usually included lidocaine
- The study injections were different from study to study
  - o Two of the studies administered only three injections; the other three administered at least six
  - o Different solutions were used in different studies, but most used glucose (12.5% the most common solution), and several used phenol and a local anesthetic (lidocaine or procaine)
- Two studies were potentially subject to confounding by having more than one difference between study and control interventions
  - o One injected the control group in an unspecified tender spot while injecting the lumbosacral ligaments in the study group; another gave the study group steroid injections in muscle tender points and manipulation, giving the control group no steroid and sham manipulation
- Separate comparisons were done for prolotherapy vs. control injections and for prolotherapy combined with spinal manipulation and exercise versus control injections
  - o When pain was reported in terms of mean pain scores at six months, there were no significant differences between prolotherapy and control
  - o When pain was reported in terms of proportions with success of treatment (50% reduction or equivalent wording), there were no significant differences between prolotherapy and control
  - o When disability was reported in terms of mean scores at six months, there were no significant differences between prolotherapy and control; the same was true for proportions of patients with more than 50% improvement in disability scores
- Two studies combined injections with other interventions; one study (Klein) gave both groups manipulation plus an exercise program, and one (Ongley) gave forceful manipulation to the prolotherapy group and sham manipulation to the control group; Ongley also injected gluteal tender points of the prolo group with lidocaine plus triamcinolone, but only injected the control group gluteal tender points with lidocaine
  - o Ongley reported significant differences in mean pain scores at six months in favor of prolo, but Klein reported no significant differences in the main analysis
  - o Ongley did not report proportions of patients with 50% pain relief at six months; Klein did report these proportions, with results in favor of prolo (77%) over control (53%)
  - o Ongley, but not Klein, reported better mean disability scores at six months for prolotherapy
  - o Klein reported better success in the prolo group when defining success as 50% improvement in pain *or* disability at six months, and

reported a significant difference for pain grid scores (pain diagrams on a transparent grid), but not for pain scores on VAS

- Commonest adverse event was pain and stiffness following injections, reported by nearly all participants in three studies

#### Authors' conclusions:

- Even with studies of generally high quality, it is difficult to interpret evidence of the efficacy of prolotherapy injections for low back pain
- The study with the most positive results (Ongley) also was potentially confounded by co-intervention bias, since the prolo group had manipulation as well as prolo
- It is possible that there is a dose-response with prolo, since studies with sustained reductions in pain and disability were the ones in which six, rather than three, injections were given, and also had 20 ml rather than 10 ml of solution
- Klein reported positive effects of prolo versus control only doing after a subgroup analysis which excluded patients with gluteal tenderness
- Some of the purported effect of prolo may be simply due to needling as a counter-irritant, rather than the injection solution
- Prolotherapy alone does not appear to have evidence of a role for the treatment of chronic low back pain

#### Comments:

- The results of one of the positive studies (Klein) appear to depend on a subgroup analysis which was not clearly part of the pre-planned protocol, and was probably done post hoc; it is reasonable to interpret Klein as an equivocal or negative study; even though the authors rated the study as high quality, they did not grade it down for this analysis, since post-hoc analysis is not explicitly a risk of bias for the Cochrane quality scale they were using
- Co-intervention (Ongley) truly remove clarity from the comparison between prolo and control injections, and the effect of combining prolo with manipulation of the SI joint, which by itself may be efficacious, weaken the evidence for prolo from this study
- The very qualified favorable interpretation of the authors toward prolo combined with co-interventions is not likely to show a clear effects of those injections

Assessment: The systematic review is of high quality, but overall supports no evidence statement in favor of prolotherapy; overall, there is good evidence that prolotherapy by itself is not an effective treatment for chronic low back pain

#### References:

Klein RG, Eek BC, DeLong B, Mooney V. A Randomized Double-Blind Trial of Dextrose-Glycerine-Phenol Injections for Chronic, Low Back Pain. *J Spinal Disorders* 1993;6:23-33.

Ongley MJ, Klein RG, Dorman TA, Eek, BC, Hubert LJ. A New Approach to the Treatment of Chronic Low Back Pain. *Lancet* 1987;2(8551):143-146.