

Evidence Based Review

Prolotherapy

Reviewer	Amanda Bowens
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Important note:

- The purpose of this evidence based review is to summarise information on the effectiveness of prolotherapy and to provide best practice advice.
- It is not intended to replace clinical judgement or be used as a clinical protocol.
- A reasonable attempt has been made to find and review papers relevant to the focus of this report; however, it does not claim to be exhaustive.
- The review has been prepared by the staff of the Evidence Based Healthcare group, ACC Research. The content does not necessarily represent the official view of ACC or represent ACC policy.
- This review is based upon information supplied up to October 2013.

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1. Summary of recommendations

- There is currently no evidence to support purchasing prolotherapy for Achilles tendinopathy.
- ACC's current recommendation not to purchase prolotherapy for low back pain or finger/thumb osteoarthritis appears to be in line with the latest evidence.
- There is limited evidence from a small number of well conducted trials that prolotherapy has some degree of effectiveness in the treatment of sacroiliac joint pain (one study), knee osteoarthritis (one study) and lateral epicondylitis (two studies); however, some of these are small, pilot-level studies
- The Research team recommends that this review be considered by the ACC Purchasing Guidance Advisory Group (PGAG), so that the recommendations on purchasing prolotherapy can be formalised and disseminated throughout ACC.

2. Background

What is prolotherapy?

Prolotherapy involves the injection of an irritant solution into a ligament, tendon or joint space¹. This is hypothesised to induce an inflammatory response that stimulates the healing process and relieves pain. The solutions used are usually non-pharmacological and non-active: dextrose or glucose solutions are common. Practitioners often inject a local anaesthetic such as lidocaine to ease any discomfort associated with the procedure.

Treatment typically involves multiple injections into painful sites repeated over several sessions²; however, treatment protocols and the solutions used vary between practitioners. Prolotherapy has been advocated for a range of disorders including back pain, knee osteoarthritis and lateral epicondylitis.

Prolotherapy was developed in the 1950s and was originally adapted from sclerotherapy, which uses irritant injections to produce inflammation and eventual thrombosis of blood vessels in the treatment of, for example, varicose veins³. Prolotherapy is sometimes referred to as proliferation therapy or regenerative injection therapy due to its claimed ability to regenerate or induce proliferation of new cells. The variant known as neural prolotherapy is based on the premise that injection of dextrose solutions reduces nerve inflammation⁴.

ACC's current position on prolotherapy

ACC reviewed the literature on prolotherapy as part of its Interventional Pain Management (IPM) guidance released in 2005⁵. Its recommendations were:

- Prolotherapy alone is not recommended for the treatment of low back pain (grade of recommendation = B, i.e. based on moderate quality evidence).
- Prolotherapy is not recommended for the treatment of finger and thumb osteoarthritis (grade of recommendation = C, i.e. based on expert opinion).

- Do not purchase prolotherapy for the treatment of low back pain or finger and thumb osteoarthritis; review the decision when more evidence becomes available.

The ACC Research team has produced this evidence based review in order to:

- Identify and review any high quality evidence on the effectiveness of prolotherapy published since the launch of the IPM guidance in 2005.
- Advise on whether the IPM recommendations on prolotherapy should be updated in the light of more recent evidence.

3. Methods

Literature search

The following databases were searched in August 2013:

- AMED
- Cochrane Library
- Google Scholar
- Embase
- Medline & Pre-Medline
- National Guideline Clearinghouse
- PubMed
- TRIP database

See Appendix 2 for information on the search strategies used.

Selection criteria

Criteria for including studies in this evidence based review were as follows:

- Study type - the following types of studies, published in English since 2005:
 - secondary research: systematic reviews (SRs), health technology assessments (HTAs), guidelines; and
 - primary studies: randomised controlled trials (RCTs) not covered by the identified secondary research
- Participants - people with musculoskeletal injuries or musculoskeletal pain
- Interventions - prolotherapy injections
- Outcomes – pain, disability, function, return to work, safety, adverse events

The following studies were excluded:

- Those available in abstract only, e.g. conference presentations
- Those dealing with autologous blood or platelet rich plasma injections (these are dealt with in other evidence based reviews by the ACC Research team)
- Those dealing solely with the injection of sclerosing solutions such as polidocanol
- Trials in progress

Grading the evidence

Studies meeting the criteria for inclusion in this evidence based review were graded using the Scottish Intercollegiate Guideline Network (SIGN) level of evidence system. For more information on the SIGN grading system see Appendix 3.

4. Findings

Eligible studies were found on the use of prolotherapy to treat Achilles tendinopathy, back pain, finger and/or thumb osteoarthritis, knee osteoarthritis and lateral epicondylitis. The findings, study quality and SIGN grades are outlined below. For more detailed analysis, see the evidence tables in Appendix 4.

Several of the SRs and other secondary studies drew their evidence from the same pool of primary studies. This was particularly apparent in the SRs for back pain. The table in Appendix 1 shows which secondary studies drew on which primary studies and may help to clarify how and to what extent the evidence overlaps.

Achilles tendinopathy

Two SRs were identified.

The most recent SR by Gross et al was published in 2013⁶. It reviewed nine RCTs on seven different injection therapies for non-insertional Achilles tendinosis, including Yelland's 2010 RCT on prolotherapy⁷. This RCT randomised 43 patients with painful Achilles tendinosis to prolotherapy with 20% glucose, eccentric loading exercises, or a combination of the two.

Gross's review noted that although most patients in Yelland's trial reported sustained improvements in pain, stiffness and overall satisfaction, there were few statistically or clinically significant differences between the three groups. The quality of the trial was rated as 14 out of a possible 21 on the Detsky scale⁸ (67%); the reviewers noted that trials scoring less than 75% are considered to be of low quality. The trial was also found to be prone to selection bias.

Gross's SR concluded that the quality of evidence on injection therapies for Achilles tendinosis is currently low and that no definite recommendations can be made on long term efficacy or the superiority of a particular therapy. This was a well conducted SR: **SIGN evidence level 1+**.

The 2010 SR and meta-analysis by Coombes et al⁹ also included the Yelland RCT⁷. These reviewers gave the RCT a PEDro score of 10 out of 13 and concluded that it did not demonstrate that prolotherapy was more effective than eccentric exercises. The SR was of high quality with a low risk of bias (only high quality RCTs with a PEDro score of 7 or more were included): **SIGN evidence level 1+**.

Back pain

One HTA and four SRs (including one Cochrane review) were identified, plus two additional RCTs.

The HTA¹⁰ and SRs^{3 11-13} were all largely based on the same five RCTs, and three of the SRs had authors in common and to some extent comprised a series of updates with slightly different inclusion criteria^{3 11 12}. The overlap between RCTs covered by the back pain SRs is illustrated in Appendix 1.

The HTA by Adams (2008)¹⁰ included SRs and case series on prolotherapy for musculoskeletal pain. The majority of the SR evidence dealt with back pain. No SIGN grade was given as it was more of a general overview/narrative review than a true SR.

The 2008 SR by Dagenais et al³ included SRs and RCTs on prolotherapy for chronic low back pain and was graded **SIGN evidence level 1+**. The 2007 Cochrane review by Dagenais et al¹² included the five “key” RCTs on prolotherapy for chronic low back pain¹⁴⁻¹⁸ and was graded **SIGN evidence level 1++**. The 2005 SR by Dagenais et al¹¹ included the five key RCTs referenced above as well as 26 observational studies on prolotherapy for spinal pain; it was graded **SIGN evidence level 1+**.

The 2005 SR by Rabago et al¹³ included six RCTs (four on back pain), two non-randomised controlled studies and 34 case series/case reports on prolotherapy for chronic musculoskeletal pain. It was graded **SIGN evidence level 1+**.

None of the secondary studies were able to pool the results of the RCTs due to heterogeneity. As they were largely based on the same primary studies, there is a fair degree of agreement in their main conclusions:

- There is conflicting evidence on the effectiveness of prolotherapy for chronic low back pain
- When used alone, it does not appear to be effective
- When combined in a multimodal treatment programme alongside other interventions such as exercise and spinal manipulation, prolotherapy may give prolonged partial relief of pain and disability
- Protocols used in the research vary widely and it is not possible to draw conclusions about the most effective regimens, dosages, solutions etc.
- Prolotherapy has a low rate of complications

Of the two RCTs on back pain, one compared the effects of intra-articular prolotherapy and steroid injections on 50 patients with sacroiliac joint pain (Kim et al 2010¹⁶). It found that, although both treatments were similarly effective in the short term, the pain relief provided by prolotherapy was significantly longer lasting (at 15 months) than that offered by steroid injections. This RCT was notable in that it used consistent, reproducible patient selection and treatment protocols; injections were given under fluoroscopic guidance. It had a low risk of bias and was therefore graded **SIGN evidence level 1+**.

The other RCT, a 2005 crossover trial by Wilkinson²⁰, examined the effects of prolotherapy on painful spinal enthesopathies (painful inflammations at the point where the ligament/tendon joins the bone). Of the 35 subjects, 30 (86%) were defined as “failed back syndrome” patients, i.e. they had undergone lumbar surgery but were still experiencing pain. The RCT concluded that prolotherapy using a phenol-glycerol solution provided better and longer lasting pain relief than

injections of local anaesthetic alone. However, there were several methodological weaknesses and the study had a high risk of bias: **SIGN evidence level 1-**.

Finger/thumb osteoarthritis

One HTA and one SR covered prolotherapy for osteoarthritis of the finger/thumb.

Both the 2005 SR by Rabago et al¹³ and the 2008 HTA by Adams¹⁰ looked at the same study: a 2000 RCT of dextrose prolotherapy versus control injections for osteoarthritic thumb and finger joints by Reeves and Hassenein²¹.

The SR notes that Reeves found significantly improved pain on movement and range of finger flexion with prolotherapy compared to control injections; however, there were no significant differences between groups for pain at rest or pain with grip. X-ray at 12 month follow up showed decreased joint space narrowing (p=.006) and improved osteophyte grade in the prolotherapy versus the control group. Rabago criticised the RCT for lack of a non-injection control group but scored it relatively highly (despite it having the smallest sample size of the six RCTs included in Rabago's SR). The SR itself was however graded **SIGN evidence level 1+** and is discussed further in the back pain section above.

The HTA by Adams¹⁰ based its conclusions on Rabago's review and made no additional comment on prolotherapy in the treatment of finger or thumb osteoarthritis. As explained in the back pain section above, the HTA took a narrative approach and was therefore not given a SIGN grade.

Knee osteoarthritis

One HTA, one SR and two additional RCTs looked at prolotherapy for knee osteoarthritis.

The 2005 SR by Rabago et al¹³ and the 2008 HTA by Adams¹⁰ each included one study on knee osteoarthritis: a 2000 RCT of prolotherapy versus control injections by Reeves and Hassenein²².

Rabago notes that pain scores, swelling, buckling episodes and flexion significantly improved in both groups in the Reeves RCT. However, in the prolotherapy group improvements were more significant and X-ray detected increased patellofemoral cartilage thickness compared to control subjects (p=0.19). Rabago argued that the Reeves RCT had several limitations, including failure to document whether participants had concomitant meniscal pathology, lack of a non-injection control group and a statistical analysis that made comparisons between groups difficult to interpret. Rabago also questioned plain X-ray's ability to quantify patellofemoral cartilage thickness effectively. The RCT scored comparatively poorly on the SR's grading scales. The SR itself was however graded **SIGN evidence level 1+** and is discussed further in the back pain section above.

The HTA by Adams¹⁰ based its conclusions on Rabago's review and made no additional comment on prolotherapy in the treatment of knee osteoarthritis. As explained in the back pain section above, the HTA took a narrative approach and was therefore not given a SIGN grade.

Turning to the primary studies: in the crossover RCT by Dumais et al (2012)²³, 45 patients were randomised to a home based exercise programme with/without regenerative injection therapy (dextrose prolotherapy), with crossover after 20 weeks (16 weeks of treatment plus a four week washout phase). Analysis suggested that 29.5% of improvements in the primary outcome (WOMAC scores of pain, stiffness and function) were attributable to prolotherapy. Nine patients (20%) dropped out, one after experiencing side effects, and the sample size was underpowered. This RCT had a high risk of bias: **SIGN evidence level 1-**.

A more recent and higher quality RCT was carried out by Rabago et al (2013)²⁴. Ninety patients with painful knee osteoarthritis of ≥ 3 months' duration were randomised to three treatment groups: home-based exercise or blinded injection with dextrose or saline. At 52 weeks, all three groups reported improved primary outcomes (WOMAC scores of pain, stiffness and function) compared with baseline. Improvements in the dextrose prolotherapy group were clinically and statistically more significant than in the other two groups. This appears to be a well conducted RCT with low risk of bias: **SIGN evidence level 1+**.

Lateral epicondylitis

Three SRs and two additional RCTs were identified.

The 2010 SR and meta-analysis by Coombes et al⁹ included one relevant RCT: Scarpone's 2008 study comparing a course of three prolotherapy injections (5% sodium morrhuate plus 50% dextrose) to saline injections in 24 subjects with chronic lateral epicondylitis. The reviewers gave the Scarpone RCT a PEDro score of 10 out of 13 and noted that although no significant effects were seen in the short term, a large reduction in pain was observed in the prolotherapy group in the intermediate term (i.e. a standardised mean difference of 2.62, 95% confidence interval 1.36 to 3.88, at 16 weeks). All subjects experienced temporary post-injection pain and two subjects in the prolotherapy group experienced local irritation versus none in the saline injection group. On the basis of this RCT, Coombes et al suggested that prolotherapy injection of hypertonic glucose and local anaesthetic is a potential therapeutic technique for lateral epicondylalgia, based on moderate evidence of improvements in the intermediate term. The Coombes SR was of high quality with a low risk of bias as only high quality RCTs with a PEDro score of 7 or more were included: **SIGN evidence level 1+**. However, it should be noted that its conclusion regarding prolotherapy was based on the results of a single relatively small RCT.

A more recent SR and network meta-analysis by Krogh et al²⁵ (2013) also included the Scarpone RCT²⁶. The Krogh SR only included RCTs comparing active injection therapies to each other or to placebo injections. Its analysis of the Scarpone RCT found that prolotherapy was more efficacious than placebo (saline) injection at 16 weeks (standardised mean difference -2.71, 95% confidence interval -4.60 to -0.82). The reviewers found that the Scarpone RCT had an overall low risk of bias, but they noted that its sample size was small and its own authors described it as a pilot study. Krogh et al concluded that there is a "**paucity of evidence from unbiased trials on which to base treatment recommendations regarding injection therapies for lateral epicondylitis**". This was a well conducted SR with a low risk of bias: **SIGN evidence level 1+**.

A 2009 SR by Rabago et al²⁷ assessed the effectiveness of four injection therapies, including prolotherapy, for lateral epicondylitis. This SR included three studies on prolotherapy: the RCT by Scarpone et al²⁶ described above, a small (n=8) RCT by Glick²⁸ and a prospective case series (n=20) by Lyftogt et al²⁹. The effect sizes in all three studies, as calculated at various time points by the reviewers, were relatively large. The reviewers concluded that there is “**strong pilot level evidence supporting the use of prolotherapy**” in the treatment of lateral epicondylitis. They do however point out that the included studies were all of small size and had other limitations. This SR was reasonably well conducted, but its reporting of results as aggregate scores and failure to assess the validity of non-RCT studies have been criticised by the UK Centre for Reviews and Dissemination (CRD)³⁰ for making it difficult to reach an independent judgement on the validity of the evidence presented. CRD suggest that these aspects of the methodology, along with the dependence on studies with small sample sizes, mean that the reviewers’ conclusions may not be reliable: **SIGN evidence level 1+/1-**.

A 2011 RCT by Carayannopoulos compared prolotherapy to corticosteroid injections in subjects with chronic (3 months to 2 years) lateral epicondylitis. Both groups reported improvements over the course of the study, but there were no significant differences between the groups (although improvements tended to be maintained in the prolotherapy group). The authors concluded that prolotherapy may be a useful alternative to corticosteroid injection, but larger studies are required. The RCT’s main flaw was that it was underpowered. Based on expected effect sizes, the authors had aimed to recruit 56 subjects but only enrolled 24, of whom only 17 actually completed the study. In addition, the number of prolotherapy injections had to be limited to two to allow direct comparison with the standard corticosteroid injection regime in the authors’ practice. The RCT had a high risk of bias: **SIGN evidence level 1-**.

A 2013 RCT by Rabago et al³¹ compared two different prolotherapy solutions (dextrose and dextrose plus sodium morrhuate) and a “wait and see” control in 27 subjects with 32 elbows affected by lateral epicondylitis. Three injections were given four weeks apart under ultrasound guidance and MRI was used to assess any post-treatment changes in symptom severity. Participants in both prolotherapy groups showed clinically significant improvements on a composite, disease-specific scale compared to the wait group at 16 weeks and improvements were maintained at 32 weeks. No changes were observed on MRI in any of the three groups. At 32 weeks there were no significant differences between the two prolotherapy groups. However, the dextrose-only solution offered some benefits over dextrose plus sodium morrhuate, as participants in the dextrose-only group appeared to improve more quickly and experienced less post-injection pain. The dextrose-only group also reported significant improvements in pain-free grip strength compared to the other two groups. Like the Scarpone trial²⁶ outlined above, the authors described this RCT as “**pilot level**” and as such it was reasonably well designed: **SIGN evidence level 1+**.

Safety

Prolotherapy appears to have a safety profile comparable with other injection procedures when performed by a skilled practitioner. The most commonly reported side effects include short term pain, stiffness and irritation at the injection site. Trial participants receiving prolotherapy for low back pain have reported a

transient increase in pain and stiffness and some cases of nausea; a few experienced severe headaches¹².

A 2006 survey of US practitioners treating back and neck pain found that the most prevalent side effects were pain (70%), stiffness (25%) and bruising (5%)³². In addition, 472 more serious adverse events were reported from an estimated median 340,000 treatment episodes. The majority (80%) were related to needle injury rather than the injected solution. Adverse events included:

Spinal headache	n=164
Pneumothorax	n=123
Temporary systemic reactions, e.g. anaphylaxis	n=73
Nerve damage	n=54
Hemorrhage	n=27
Non-severe spinal cord insult, e.g. temporary paralysis	n=9
Disk injury	n=2

Hospitalisation was required in 69 cases; the most common reason was pneumothorax (n=48). In five cases adverse events led to permanent injury secondary to nerve damage. The survey authors noted that prolotherapy has become safer over time; the use of solutions associated with serious adverse events has been discontinued in favour of dextrose solutions which are largely perceived to be safe.

The literature search for this ACC brief report identified one recent case report of a serious adverse event associated with prolotherapy. A 49 year old Korean man experienced a cervical spinal cord injury (ASIA impairment scale level E leading to persistent pain but no neurological/motor impairment) after receiving 15% dextrose injections into the shoulder, elbow and near right C5 nerve root to treat tendinitis. This underlines the importance of skilled and experienced practitioners, particularly when injections are administered to the spinal region.

5. Additional information

Current guideline recommendations on prolotherapy

The literature search identified four guidelines (including the ACC IPM guideline⁵) that make recommendations on prolotherapy in the treatment of six different conditions – the recommendations are summarised in the table below.

The majority either recommend against the use of prolotherapy or are unable to make a recommendation due to insufficient evidence. The exceptions are a Canadian guideline which notes that it may be useful for selected back pain patients as part of a therapeutic programme alongside other interventions and a US guideline which recommends it for selected patients with patellar tendinopathy. However it is possible that the latter recommendation applies to sclerotherapy rather than prolotherapy injections.

Table: summary of guideline recommendations on prolotherapy

Guideline	Recommendation	Strength of evidence
Achilles tendinopathy		
American College of Occupational and Environmental Medicine (ACEOM V.3, 2011 ³³)	No recommendation for or against the use of prolotherapy for the treatment of chronic Achilles tendinopathy	Recommendations could not be made due to insufficient evidence
Back Pain		
ACC Interventional Pain Management guidance (ACC 2005 ⁵)	Prolotherapy alone is not recommended for the treatment of low back pain	Grade B recommendation (i.e. supported by fair quality evidence)
American College of Occupational and Environmental Medicine (ACEOM V.3, 2011 ³³)	Prolotherapy injections are not recommended for treatment of acute, subacute, or chronic low back pain or any radicular pain syndrome (including sciatica)	Grade C recommendation (i.e. limited evidence-base: at least one study of moderate quality)
American Pain Society guideline on interventional therapies for low back pain (Chou et al 2009 ³⁴)	Prolotherapy not recommended for patients with persistent nonradicular low back pain	Strong recommendation based on “ <i>good evidence that prolotherapy is ineffective for nonspecific low back pain</i> ” ³⁵ (i.e. the 5 RCTs included in the Cochrane review by Dagenais et al ¹²)
Toward Optimized Practice guideline (Canada) (TOP 2011 ³⁶)	<u>Sole treatment:</u> Prolotherapy is not recommended as a sole treatment for chronic low back pain	Systematic review
	<u>Adjunct treatment:</u> Prolotherapy may be useful for carefully selected and monitored patients who are participating in an appropriate program of therapeutic exercise and/or manipulation/mobilization	Expert opinion
Finger & thumb osteoarthritis		
ACC Interventional Pain Management guidance (ACC 2005 ⁵)	Prolotherapy is not recommended for the treatment of finger and thumb osteoarthritis	Grade C recommendation (i.e. supported by expert opinion only)
American College of Occupational and Environmental Medicine (ACEOM V.3, 2011 ³³)	No recommendation for or against the use of prolotherapy to treat finger or thumb osteoarthritis	Recommendations could not be made due to insufficient evidence
Knee osteoarthritis		
American College of Occupational and Environmental Medicine (ACEOM V.3, 2011 ³³)	Prolotherapy injections are not recommended for the treatment knee osteoarthritis	Grade C recommendation (i.e. limited evidence-base: at least one study of moderate quality)

Lateral epicondylalgia		
American College of Occupational and Environmental Medicine (ACEOM V.3, 2011 ³³)	No recommendation for or against the use of prolotherapy for the treatment of lateral epicondylalgia	Recommendations could not be made due to insufficient evidence
Patellar tendinopathy		
American College of Occupational and Environmental Medicine (ACEOM V.3, 2011 ³³)	Prolotherapy injections are recommended to treat chronic patellar tendinopathy in select patients	“Insufficient evidence” (this recommendation appears to be based on expert opinion & an RCT by Hoksrud et al (2006 ³⁷), which deals with sclerosing polidocanol injections rather than prolotherapy ¹)

Overseas agencies’ policies on prolotherapy

In the United States, Aetna (a major managed health care company) considers prolotherapy experimental for all indications due to inadequate evidence of effectiveness³⁸. Similarly, United Healthcare regards prolotherapy as unproven³⁹ and Blue Cross Blue Shield considers it investigational⁴⁰. The Medicare social insurance programme does not currently cover prolotherapy, but has not reviewed the evidence or updated its decision since 1999⁴¹.

There are anecdotal reports that workers’ compensation schemes in the United States fund prolotherapy to treat covered injuries and that the National Health Service in the United Kingdom may fund it as part of a clinical trial or on a case by case basis, but these could not be confirmed.

In Quebec, the health technology assessment agency INESSS recently carried out a review of prolotherapy for chronic musculoskeletal conditions; it could not be included in this ACC brief report as the full text is only available in French. The INESSS review concluded that neither the scientific evidence nor the balance of risk and benefit currently support the use of prolotherapy⁴². It also argues that further research with human subjects is unethical as the proposed mechanism of action for prolotherapy is “speculative at best”.

American Association of Orthopaedic Medicine’s position

The American Association of Orthopaedic Medicine (AAOM) is highly supportive of prolotherapy. It organises regular prolotherapy training events throughout the US. Physicians who complete the training are awarded an AAOM certificate in prolotherapy. In 2004, the AAOM presented a position statement⁴³ in support of prolotherapy to the California Technology Assessment Forum (CTAF), which

¹ The recommendation notes that prolotherapy is indicated for “***Athletes with chronic patellar tendinopathy with neovascularization corresponding to the painful area that is unresponsive to other treatments including NSAID(s) and activity modification. Whether these injections are appropriate for others, including workers, is unclear. Ultrasound guidance is recommended for accomplishing the injections***”.

evaluates new and emerging medical technologies. However, after reviewing the scientific evidence available at the time, CTAF decided that prolotherapy did not meet three of its five assessment criteria⁴⁴.

6. Discussion

Nature and quality of the evidence

The quality of the evidence is variable and, as there are relatively small numbers of studies on each condition, it is difficult to draw reliable conclusions. The amount of evidence that is genuinely “new” (i.e. post-2005) is limited; several of the SRs published since 2005 actually draw on older primary studies that have already been considered by ACC when developing its IPM recommendations on back pain and finger/thumb osteoarthritis. The SRs also overlap to a great extent in terms of the primary studies they cover.

Prolotherapy treatment regimens described in the studies vary with respect to solutions, dosages, injection techniques and number of sessions. Patient selection criteria and control treatments also vary. Some authors argue that more research is needed with non-injection controls, as placebo injections or even dry needling may provoke an inflammatory response through expansion effects or needle trauma^{13 24}.

Other points emerging from the literature include:

- There is evidence that subjects who receive prolotherapy combined with other treatments such as spinal manipulation or exercise do better than those receiving prolotherapy alone^{6 12}
- Some authors argue that studies to date have relied too heavily on subjective outcomes and more use should be made of imaging assessments and biomarkers of tissue healing⁴⁵; however, in studies that have used imaging assessments, these have been criticised^{22 13} or have been inconclusive³¹
- The majority of overseas guidelines that have made recommendation on prolotherapy either recommend against it or are unable to make a recommendation due to insufficient evidence
- Prolotherapy appears to be relatively safe.

Limitations of the evidence based review

The exclusion of foreign language material, conference presentations and trials in progress may have led to relevant evidence being missed.

7. Conclusions & recommendations

The evidence statements below attempt to summarise the body of evidence for each of the five conditions covered in this review. The recommendations for purchasing discuss how this evidence might be translated into ACC-wide policies on funding prolotherapy for clients.

Evidence statements

Achilles tendinopathy: two recent, well-conducted systematic reviews/meta-analyses^{6,9} concluded that the evidence (from one medium quality RCT⁷) does not demonstrate that prolotherapy is more effective than eccentric loading exercises.

Back pain: four well-conducted SRs^{3,11-13} concluded that the evidence on the efficacy of prolotherapy for chronic low back pain is conflicting. When used alone it does not appear to be effective, but when combined with other interventions, such as spinal manipulation or exercise, it may contribute to sustained relief of pain and disability. This evidence was largely drawn from a core group of five RCTs published before 2005¹⁴⁻¹⁸. A recent, well conducted RCT¹⁹ found that prolotherapy offered longer lasting pain relief than steroid injections in patients with sacroiliac joint pain; all injections were given under fluoroscopic guidance using consistent treatment protocols.

Finger/thumb osteoarthritis: one well-conducted SR¹³ found evidence (from one high quality RCT²¹ published in 2000) that prolotherapy was more effective than control injections at improving pain on movement and range of finger flexion. However, the same RCT was assessed as part of ACC's IPM guidance and found to be of medium to high quality, but underpowered and subject to losses to follow up. In the expert opinion of the IPM guideline development group, on the basis of the available evidence, prolotherapy could therefore not be recommended for finger/thumb osteoarthritis.

Knee osteoarthritis: one well-conducted SR¹³ found evidence (from one low to medium quality RCT²² published in 2000) that prolotherapy was more effective than control injections. A recent, well conducted RCT²⁴ found that prolotherapy was more effective than saline injections or home exercise.

Lateral epicondylitis: two well conducted SRs^{9,25,27} found evidence (from one high quality but small pilot RCT²⁶) that prolotherapy with a dextrose-sodium morrhuate solution was more effective than saline injections. A less well conducted SR²⁷ (which included the RCT mentioned above plus an additional very small RCT²⁸ and a prospective case series²⁹) concluded that there is “**strong pilot-level evidence**” supporting the use of prolotherapy. A recent, well conducted pilot RCT³¹ found that prolotherapy with either a dextrose or dextrose-sodium morrhuate solution was more effective than “**watchful waiting**”; dextrose appeared preferable to dextrose-sodium morrhuate in terms of speed of improvement and post-injection pain.

Recommendations for purchasing

There is currently no evidence to support purchasing prolotherapy for Achilles tendinopathy.

On the basis of the evidence identified by this update, it appears that ACC's 2005 IPM recommendation not to purchase prolotherapy for low back pain or finger/thumb osteoarthritis is still appropriate.

There is limited evidence on the use of prolotherapy for sacroiliac joint pain (one well conducted RCT¹⁹), (knee osteoarthritis (one well conducted RCT²⁴)) and lateral

epicondylitis (two well conducted RCTs^{26 31}; both were small and described by their authors as pilot studies). It may be prudent to wait until more definitive research is available before making purchasing recommendations on these two conditions.

The Research team recommends that this review be considered by the ACC Purchasing Guidance Advisory Group (PGAG), so that the recommendations on purchasing prolotherapy can be formalised and disseminated throughout ACC.

8. Acknowledgements

Thanks to Mark Ayson and Meagan Stephenson, colleagues in the ACC Research team, for their helpful advice on this document, and to Dr Hamish Osborne for providing external peer review. Thanks also to Helen Brodie in ACC Information & Knowledge Services for valuable assistance in obtaining copies of the studies included in this review.

Appendices

Appendix 1: evidence overlap - RCTs covered by included reviews

(i) Back pain, finger/thumb osteoarthritis & knee osteoarthritis

<i>This review</i> ⇨ <i>covers these RCTs</i> ⇩	ACC guidance (IPM) 2005 ⁵	Adams 2008 ¹⁰	Rabago 2005 ¹³	Dagenais 2008 ³	Dagenais 2007 ¹²	Dagenais 2005 ¹¹
	Back pain & finger OA	Back pain & finger OA & knee OA	Back pain only			
Dechow 1999 ¹⁴	●		●	●	●	●
Klein 1993 ¹⁵	●		●	●	●	●
Mathews 1987 ¹⁶				●	●	●
Ongley 1987 ¹⁷	●		●	●	●	●
Reeves 2000 ²¹ (finger/thumb OA)	●		●			
Reeves 2000 ²² (knee OA)			●			
Yelland 2004 ¹⁸	●		●	●	●	●
& these reviews ⇩						
Dagenais 2008 ³		●				
Dagenais 2007 ¹²				●		
Dagenais 2005 ¹¹				●		
Rabago 2005 ¹³		●		●		
Yelland 2004 ⁴⁶	●			●		
Plus non-RCTs ⇩						
Non-controlled trials & case series		●	●			●

(ii) Tendinopathies

<i>This review</i> ⇨	Gross 2013 ⁶	Coombes 2010 ⁹	Krogh 2013 ²⁵	Rabago 2009 ²⁷
<i>covers these RCTs</i> ⇩				
	Achilles tendinosis	Achilles tendinosis & lateral epicondylalgia	Lateral epicondylalgia only	
Glick 2006 ²⁸				●
Scarpone 2008 ²⁶		●	●	●
Yelland 2010 ⁷	●	●		
<i>Plus non RCTs</i> ⇩				
Lyftogt 2007 ²⁹ (prospective case series)				●

Appendix 2: search strategies

The core search strategy (see below) was developed for the Medline database and adapted for use with the other databases.

For example, for databases with a different subject indexing system to Medline (e.g. Embase), equivalent subject terms were substituted.

Database-specific filters were used, where possible, to limit retrieval to reviews and randomised controlled trials.

1. prolotherap\$.mp.
2. "regenerat\$ inject\$ therap\$".mp.
3. ((prolifera\$ or scleros\$) and inject\$).mp.
4. exp *Pain/
5. 3 and 4
6. exp Glucose/ad [Administration & Dosage]
7. exp Glycerol/ad [Administration & Dosage]
8. exp Phenol/ad [Administration & Dosage]
9. exp Sclerosing Solutions/ad [Administration & Dosage]
10. exp Irritants/ad [Administration & Dosage]
11. exp *Injections/
12. or/6-10
13. 11 and 12
14. 1 or 2 or 5 or 13
15. limit 14 to (humans and yr="2004 - 2013")

Appendix 3: SIGN levels of evidence

SIGN criteria for classifying studies.	
Score	Design
1++	High quality meta-analyses, systematic review of RCTs, or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs or RCTs with a high risk of bias
2++	High quality systematic reviews of case-control or cohort studies. High quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal.
3	Non-analytic studies
4	Expert opinion

Available from Scottish Intercollegiate Guidelines Network (SIGN) website, see www.sign.ac.uk/

Appendix 4: evidence tables

Evidence table 1: Achilles tendinopathy - systematic reviews A – Z by author										
Study	Inclusions	Interventions	Outcomes & results	Comments & level of evidence						
Systematic review & meta analysis of RCTs on corticosteroid & other injections for management of tendinopathies (Coombes et al 2010 ⁹)	<p>Inclusion criteria: RCTs scoring >50% (i.e. at least 7/13) on a modified PEDro scale</p> <p>Included studies: 41 RCTs including one (Yelland et al 2010⁷, n=43) on prolotherapy for painful mid-portion Achilles tendinosis. This 3-arm RCT randomised 43 patients to a 12 week programme of 20% glucose injections, eccentric loading exercises (ELE) or a combination of the two. Subjects were followed up for 12 months. The RCT was carried out in five Australian primary care centres.</p>	<p>Interventions: Peritendinous injections of corticosteroids or other agents</p> <p>Controls: Placebo or non-surgical interventions</p>	<p>Outcomes assessed: Primary outcome: protocol-defined pain score in the short, intermediate & long term. Other outcomes: function, patient satisfaction, adverse events</p> <p>Results: The reviewers scored the Yelland RCT 10 out of 13 (77%) on the PEDro scale. They calculated the overall improvements demonstrated for prolotherapy vs. ELE (in terms of pain, stiffness & function) over the short, intermediate & long term as follows:</p> <p><u>Overall improvement, relative risk (95% confidence interval):</u></p> <table border="0"> <thead> <tr> <th><u>Short term</u></th> <th><u>Intermediate</u></th> <th><u>Long term</u></th> </tr> </thead> <tbody> <tr> <td>1.69 (0.92 to 3.12)</td> <td>1.27 (0.80 to 2.02)</td> <td>1.00 (0.72 to 1.39)</td> </tr> </tbody> </table> <p>No adverse events were reported in the Yelland RCT apart from temporary post-injection discomfort</p> <p>Conclusions: The reviewers concluded that outcomes did not differ significantly in the short, intermediate or long term; therefore the RCT did not demonstrate that prolotherapy was more effective than ELE in the treatment of Achilles tendinosis.</p>	<u>Short term</u>	<u>Intermediate</u>	<u>Long term</u>	1.69 (0.92 to 3.12)	1.27 (0.80 to 2.02)	1.00 (0.72 to 1.39)	<p>The reviewers appear to have combined improvement after prolotherapy with improvement after prolotherapy + ELE and compared this against improvement following ELE alone</p> <p>This was a well conducted systematic review & meta-analysis with a low risk of bias as only high quality RCTs with a PEDro score of 7 or more were included: SIGN evidence level 1+</p>
<u>Short term</u>	<u>Intermediate</u>	<u>Long term</u>								
1.69 (0.92 to 3.12)	1.27 (0.80 to 2.02)	1.00 (0.72 to 1.39)								

Study	Inclusions	Interventions	Outcomes & results	Comments & level of evidence
<p>Systematic review of injectable treatments for Achilles tendinosis (Gross et al 2013⁶)</p>	<p>Inclusion criteria: RCTs, or cohort studies with a comparative control group, on the efficacy of injectable treatments for people with non-insertional Achilles tendinosis</p> <p>Included studies: Nine RCTs on seven different treatments including Yelland et al's 2010 study on prolotherapy for Achilles tendinosis⁷ (see evidence table for the SR by Coombes et al, above, for details of this RCT)</p>	<p>Interventions: Prolotherapy, platelet-rich plasma, sclerosing agents, protease inhibitors, autologous blood injection, hemodialysate & corticosteroids</p> <p>Controls: ELE, control injections</p>	<p>Outcomes assessed: Various, including pain & function measured on VISA-A (tool developed specifically for Achilles tendinopathy), pain assessed on visual analogue scale, patient satisfaction & cost effectiveness</p> <p>Results: <u>Prolotherapy:</u> The reviewers note that although most patients in the Yelland RCT reported sustained improvements in VISA-A scores, there were few statistically or clinically significant differences between the three groups: “<i>all groups had improved levels of pain and stiffness with similar gains in patient satisfaction</i>”. They rate the quality of the RCT as 14 out of a possible 21 (67%) on the Detsky⁸ scale and note that trials scoring less than 75% are considered to be of low quality. They also find the RCT to be prone to selection bias.</p> <p>Cost effectiveness: the RCT found that compared with ELE alone, prolotherapy cost an additional \$90 and combined treatment cost an additional \$191. However, for these extra costs, an additional 13% of patients had VISA-A improvements > 20 points</p> <p>Conclusions: The reviewers conclude that the quality of evidence on injection therapies for Achilles tendinosis is currently low and that no definite recommendations can be made on long term efficacy or the superiority of a particular therapy</p>	<p>The methodological quality of the nine included RCTs was limited; only one (on platelet rich plasma) scored > 75% on the Detsky scale</p> <p>Variability between studies made direct comparisons difficult & there are too few studies on each treatment to support robust meta-analysis</p> <p>The review authors acknowledge possible language & publication biases</p> <p>Apart from a few errors in the write up, this appeared to be a reasonably well conducted systematic review: SIGN evidence level 1+</p>

Evidence table 2.1: back pain, systematic reviews & health technology assessments A – Z by author

Study	Inclusions	Interventions	Outcomes & results	Comments & level of evidence
<p>Health technology assessment (HTA) of prolotherapy for musculoskeletal pain</p> <p>Carried out for US Department of Veterans' Affairs (Adams 2008¹⁰)</p>	<p>Inclusion criteria:</p> <p>“<i>Most recent</i>” systematic reviews (SRs) plus any additional primary studies with ≥10 subjects in each treatment arm</p> <p>Included studies:</p> <p>The authors found two SRs (Dagenais 2008³ & Rabago 2005¹³) plus three additional primary studies (all case series)</p>	<p>Interventions:</p> <p>Prolotherapy injections for musculoskeletal pain; the majority of the SR evidence applied to low back pain; evidence for finger & knee OA came respectively from 2 RCTs reported in Rabago’s SR¹³</p> <p>Controls:</p> <p>Various, including control injections</p>	<p>Note: the RCTs included in the two SRs overlapped to a great extent. In addition, the Dagenais 2008 SR itself included both the Rabago 2005 SR and the Cochrane review below (Dagenais 2007¹²).</p> <p>See evidence tables below for more information on the included SRs Rabago 2005¹³ & Dagenais 2008³ (control treatments, outcomes, conclusions etc); see Appendix 2 for details of how the various SRs and RCTs referred to in this ACC brief report overlap).</p> <p>Conclusions :</p> <p>Results of recent SRs are inconclusive; new evidence from case series adds little. Most research to date has focused on back pain and knee osteoarthritis, with varying results. Sample sizes have been too small to form a basis for national policy decisions. More attention needs to be paid to appropriate control treatments; RCTs have focused on control injections, which may stimulate a response regardless of the injectant used, resulting in similar improvements across all study arms. Other RCTs have used treatment regimens that make it difficult to attribute improvements to prolotherapy alone.</p> <p>Prolotherapy alongside conservative interventions (e.g. physiotherapy) appears to offer some pain relief in patients with low back pain for whom other treatments have failed, but its independent role in such patients has not been established. Due to the growing popularity of prolotherapy, research is required to determine indications, patient selection criteria, safety profile & optimum injectants, dosages and schedule (particularly in the case of back pain, given its prevalence in Veterans’ Affairs clients).</p>	<p>Thorough & inclusive literature search yielded a surprisingly small number of papers</p> <p>The quality of the included studies was not assessed; the author’s conclusions do however appear to be an accurate reflection of the findings of the included SRs</p> <p>This report is a general overview rather than a true critical HTA/SR, therefore no SIGN grade was given</p>

Study	Inclusions	Interventions	Outcomes & results	Comments & evidence level
Systematic review of prolotherapy for chronic low back pain (Dagenais et al 2008 ³)	<p>Inclusion criteria: Guidelines, SRs & RCTs published in English from 1997 to 2007; RCTs had to be of >3 months' duration & report clinically relevant outcomes, e.g. pain or function</p> <p>Included studies: 4 SRs^{11-13 46} and 5 RCTs¹⁴⁻¹⁸ (same RCTs as those covered in Cochrane review (Dagenais 2007¹²) and in Dagenais 2005¹¹ below; high degree of overlap between studies - the SRs each covered more or less the same RCTs</p>	<p>Interventions: Prolotherapy injections for chronic low back pain; various protocols</p> <p>Controls: Various; RCTs used control injections</p>	<p>Outcomes assessed: Pain, disability</p> <p>Results: Primary study protocols vary widely, results cannot be combined; possible dose-response relationship with dextrose/glycerine/ phenol/lidocaine solutions (negative results noted in lower dose RCTs) & no evidence to support dextrose alone; 2 RCTs where prolotherapy was administered with cointerventions had positive results^{15 17} whilst RCTs with prolotherapy alone had negative results^{14 16 18}</p> <p>Conclusions: Prolotherapy has a long history, a reasonable (but not proven) theoretical basis, a low complication rate & conflicting evidence of efficacy; this may be partly explained by dose-response effects or the combination with cointerventions (i.e. spinal manipulation & exercise). May be worth considering protocol based on 2 positive RCTs* for patients with low back pain refractory to other approaches; no evidence for prolotherapy alone</p> <p>* 20-30ml dextrose/glycerine/phenol/lidocaine plus spinal manipulation & exercise weekly for 6 weeks</p>	<p>Methodology of studies was discussed but no formal grades were given</p> <p>Authors' conclusions are a fair reflection of the 5 included RCTs</p> <p>SIGN evidence level 1+</p>

Study	Inclusions	Interventions	Outcomes & results	Comments & level of evidence
Cochrane review of prolotherapy injections for chronic low	<p>Inclusion criteria: RCTs & quasi RCTs</p> <p>Included studies:</p>	<p>Interventions: Prolotherapy injections (glucose, glucose + glycerine or</p>	<p>Outcomes assessed: All five studies assessed pain and disability levels at six months. Four studies measured the proportion of participants with >50% reduction in pain or disability. Four studies used validated outcome measures whereas one (the lowest rated for quality) just</p>	<p>The review authors conclude that repeated ligament injections, irrespective of the solution used, may give prolonged partial relief of</p>

back pain (Dagenais et al 2007 ¹²)	Five high quality studies (RCTs) involving 366 adult patients with low back pain lasting longer than three months Note: the literature search was re-run end July 2009 and no new RCTs were identified	dextrose + glycerine plus local anaesthetic with/without phenol) into lumbo-pelvic ligaments; injections were given alone or in combination with other treatments; Controls: Control injections	used numerical and visual analogues scales ¹⁶ Results: Three RCTs (206 participants) found that prolotherapy injections alone were no more effective than control injections. Two RCTs (160 participants) found that prolotherapy given along with spinal manipulation, exercise and other co-interventions was more effective than control injections. One of these RCTs reported a significant difference in mean pain and disability scores at six months. Both RCTs reported a significant difference in the proportion of participants experiencing > 50% reduction in pain or disability. Conclusions: There is conflicting evidence on the effectiveness of prolotherapy for chronic low back pain. When used alone, it is not an effective treatment. When combined with spinal manipulation, exercise and other co-interventions, prolotherapy may improve pain and disability.	pain and disability as part of a multimodal treatment programme combined with spinal manipulation and exercise. Meta-analysis was not possible due to clinical heterogeneity. This and the use of co-interventions in two studies may confound the conclusions; hence the role of prolotherapy in the treatment of low back pain is still not clear. High quality systematic review of RCTs SIGN evidence level 1++
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Study	Inclusions	Interventions	Outcomes & results	Comments & level of evidence
Critical review of literature on prolotherapy for spinal pain (Dagenais et al 2005 ¹¹)	Inclusion criteria: English language clinical studies (≥5 patients, any design) on prolotherapy for any type of spinal pain Included studies: 5 RCTs on low back pain (same as those	Interventions: Prolotherapy (defined here as “ <i>intra-ligamentous injection of sclerosing solutions</i> ”); protocols varied widely between studies Controls:	For outcomes & results of the 5 included RCTs see table for Cochrane review (Dagenais 2007) above ¹² Other findings: Authors argue that well designed RCT by Yelland ¹⁸ suggests dextrose alone is of no value for spinal pain (when compared with more commonly used dextrose/glycerine/phenol or “ <i>P2G</i> ” solutions) Adverse effects reported in the 31 studies included	Authors aimed to comprehensively review the literature & deliberately avoided excluding poorly designed studies as “ <i>they are often cited as evidence by clinicians</i> ” Methodology of studies was discussed but no formal grades

	covered in Cochrane review above (Dagenais 2007 ¹²) plus 26 observational cohort studies covering over 3000 patients	Control injections (in the RCTs)	temporary pain/stiffness at the injection site Conclusions: Prolotherapy should be viewed in same light as other treatments for spinal pain that are supported by cohort studies or conflicting RCTs. Future trials should focus on the most widely used protocols (e.g. P2G solutions) in well-defined, homogenous subject samples	were given Authors' conclusions are a fair reflection of the 5 included RCTs SIGN evidence level 1+
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Study	Inclusions	Interventions	Outcomes & results	Comments & level of evidence
Systematic review of prolotherapy for chronic musculo-skeletal pain (Rabago et al 2005 ¹³)	<p>Inclusion criteria: All published studies involving humans with any type of musculo-skeletal pain or soft tissue injury</p> <p>Included studies: 34 case reports & case series, 2 non randomised controlled trials, 6 RCTs; most subjects had low back pain, sacro-iliac dysfunction or osteoarthritis (metacarpal or knee) The RCTs involved</p>	<p>Interventions: Prolotherapy injections; various administration protocols, generally dextrose with/without lidocaine or phenol-glucose-glycerine. In some studies injected steroids, spinal manipulation and exercise were given before prolotherapy</p> <p>Controls: Various, including control injections (e.g. lidocaine alone, saline, saline/lidocaine) &</p>	<p>Outcomes assessed: Response rates as defined in the studies, including % of subjects with >50% improvement in pain/disability score, subjective pain assessment, disability, joint flexion & hand grip</p> <p>Results: The non-RCTs reported positive subjective outcomes across all conditions, but the results of the 6 RCTs were conflicting: <u>Osteoarthritis (OA)</u>, 2 RCTs: One RCT (metacarpal joint OA, n=27)²¹ found prolotherapy significantly improved pain on movement & range of finger flexion compared to control injection, but there was no significant difference between groups for pain at rest or grip. X-ray at 12 month follow up showed decreased joint space narrowing (p=.006) & improved osteophyte grade in prolotherapy group vs. controls. The reviewers scored this RCT 5/5 on the Jadad scale & 9/9 on the Delphi assessment The other RCT (knee OA, n=68)²² found that both prolotherapy & control injections significantly improved pain scores, swelling, buckling episodes and flexion. Improvements were more significant in the prolotherapy group; also, lateral patellofemoral cartilage thickness</p>	<p>Study question and inclusion criteria were very broadly defined & the literature search was thorough and inclusive</p> <p>Quantitative synthesis not possible due to differing protocols across studies</p> <p>Although the authors graded the RCTs relatively highly using aggregate scoring systems, they identified “<i>significant methodological limitations</i>” in all of them; there was little consistent detail on the individual components of</p>

	439 adults & were of high quality, scoring 4-5 out of 5 on the Jadad scale and 7-9 out of 9 on the Delphi internal validity assessment	conservative therapies	<p>showed greater increase at 12 month follow up in prolotherapy group vs. controls (p=0.19). The reviewers scored this RCT 4/5 on the Jadad scale & 7/9 on the Delphi assessment</p> <p><u>Low back pain</u>, 4 RCTs:</p> <p>2 RCTs found that prolotherapy preceded by injected steroids, manipulation & exercise significantly improved pain & disability (% of subjects with >50% improvement compared with controls = 88% versus 39% for pain reduction in one RCT, 77% versus 53% for reduction in pain score or disability in the other); in both these RCTs the control treatment was saline/lidocaine injection and prolotherapy was given along with manipulation, exercise and/or steroids. The other 2 RCTs (including the largest & highest quality one¹⁸) found no difference between prolotherapy alone and the control treatment.</p> <p>Conclusions:</p> <p>High quality evidence supporting the use of prolotherapy in the treatment of musculoskeletal pain or sport-related soft tissue injuries is lacking. Results are conflicting and the studies have methodological limitations.</p>	<p>quality</p> <p>Possible confounding effects of the co-interventions in two of the low back pain RCTs were not really addressed</p> <p>In terms of its analysis of available RCTs only, this was a well conducted systematic review that adequately reflects the conflicting nature of the evidence</p> <p>SIGN evidence level 1+</p>
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Evidence table 2.2: back pain, RCTs A – Z by author				
Study	Inclusions	Interventions	Outcomes & results	Comments & level of evidence
RCT of intra-articular prolotherapy v. steroid injections for sacroiliac (SI) joint pain (Kim et al	<p>Inclusion criteria:</p> <p>Patients with SI joint pain (confirmed by positive response to anaesthetic block) lasting ≥3 months</p>	<p>Interventions:</p> <p>Intra-articular prolotherapy: 2.5ml 25% dextrose injected into SI joint (n=23)</p>	<p>Outcomes assessed:</p> <p>Pain (on numeric rating scale NRS) & disability (on Oswestry disability index ODI) assessed at baseline & 2 weeks after completion; main outcome measure = “cumulative incidence of sustained pain relief” defined as maintenance of ≥50% improvement in baseline NRS at 6, 10 & 15 months</p>	<p>Note: sample size based on power calculation was originally set at 45 in each group; but after interim analysis, recruitment was stopped due to significantly better results in the</p>

<p>2010¹⁹); conducted at an outpatient clinic in Korea</p>	<p>& resistant to medical treatment</p> <p>Included subjects:</p> <p>50 patients were enrolled & randomised; one in each group was lost to follow-up; groups were comparable at baseline</p>	<p>Controls:</p> <p>Triamcinolone acetonide SI joint injection (n=25)</p> <p>Injections were given every other week up to a maximum of 3 injections; if a patient's symptoms were improved by >90% on the 2nd or 3rd visit, the next procedure was cancelled</p> <p>Injections were given under fluoroscopic guidance</p>	<p>Results:</p> <p>NRS & ODI significantly improved from baseline at 2 weeks in both groups, but no significant difference between groups</p> <p>Incidence of ≥50% pain relief at 6 months was 63.6% in the prolotherapy group v. 27.2% in the steroid group</p> <p>Incidence of ≥50% pain relief at 15 months was 58.7% (95% CI 37.9% - 79.5%) in the prolotherapy group v. 10.2% (95% CI 6.7% - 27.1%) in the steroid group; this was a statistically significant difference (p <0.005)</p> <p>Conclusion:</p> <p>Intra-articular prolotherapy provided significant relief of sacroiliac joint pain & its effects lasted longer than those of steroid injections</p> <p>Authors argue that their intra-articular prolotherapy approach for SI pain (i) reduces variability in patient selection & injection technique; (ii) treats ventral structures inaccessible to ligament prolotherapy/RF denervation; (iii) is more comfortable for the patient than ligament prolotherapy/RF denervation</p>	<p>prolotherapy group</p> <p>Clear, consistent & reproducible patient selection & treatment protocols</p> <p>Patients & assessing physicians blind to treatment allocation; injections administered by a physician not involved in study</p> <p>RCT with a low risk of bias</p> <p>SIGN evidence level 1+</p>
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Study	Inclusions	Interventions	Outcomes & results	Comments & level of evidence
<p>Single blind crossover RCT of injection therapy for enthesopathies causing axial spine pain (Wilkinson 2005²⁰); study</p>	<p>Inclusion criteria:</p> <p>Patients referred for possible neurosurgery for painful enthesopathies diagnosed by histology, palpation & confirmed by</p>	<p>Intervention:</p> <p>1% lidocaine test injection to tender area followed by 0.5% bupivacaine plus 1% phenol & 10% glycerol</p> <p>Controls:</p>	<p>Outcomes assessed:</p> <p>Patient rating of pain relief as excellent, good, partial or poor obtained at follow up visits (“<i>clinical assessment</i>”); duration of pain relief; patient self-rating of medication usage, activities of daily living, ability to work and socialise & overall assessment of impact of therapy via questionnaire</p> <p>Results:</p>	<p>Crossover & lack of a standardised protocol for timing of injections makes the results hard to interpret</p> <p>Injection sites were not clearly described and results were not</p>

<p>was conducted at the author's private practice in the US</p>	<p>anaesthetic injection</p> <p>Included subjects:</p> <p>35 patients aged 24-73, average age 50; 14 male, 21 female; 30 (86%) were "failed back syndrome" patients, i.e. they had undergone prior lumbar surgery but still experienced severe axial pain; 27 enthesopathies were located at the posterior iliac crest with the remainder at the lumbar (n=1), thoracic (n=6) & cervical (n=1) spine</p>	<p>1% lidocaine test injection to tender area followed by 0.5% bupivacaine</p> <p>Patients requested repeat injections when pain relief subsided</p> <p>Crossover:</p> <p>Patients experiencing inadequate relief 7-14 days after initial injection could request a blinded 2nd injection of the alternative solution"; in addition, patients requesting a repeat injection after 6 weeks were re-randomised to either prolotherapy or control</p>	<p>Clinical assessment: 80% who received prolotherapy reported good-to-excellent relief v. 47% who received anaesthetics alone; results were rated as poor after 11% of prolotherapy and 45% of anaesthetic injections respectively; the difference reached statistical significance</p> <p>Questionnaire: 66% reported good-to-excellent relief with prolotherapy v. 34% with anaesthetics alone; poor results were reported after 6% of prolotherapy v. 21% of anaesthetic injections; the difference reached statistical significance</p> <p>Mean/median duration of persistent pain relief: 2.4/1.57 month with prolotherapy v. 1.8/0.75 months with anaesthetic</p> <p>Crossover: 17 alternative injections were given at patients' request due to lack of benefit from the first injection (12 following anaesthetics alone & 5 following prolotherapy)</p> <p>At the end of the trial, only 4 of the 35 patients continued to pursue the option of further surgery, while 29 requested continuing periodic injections</p> <p>Conclusion:</p> <p>In failed back syndrome patients, phenol-glycerol prolotherapy provides better & longer lasting pain relief than injection with anaesthetics alone; however, improvement generally lasted "only a few months"</p>	<p>grouped by site of pain/injection</p> <p>This RCT was excluded from the Cochrane review by Dagenais et al¹² for the reasons stated above</p> <p>Not clear whether a crossover design is suitable here due to possible carry-over effects</p> <p>Lack of validated outcome measures; treating/assessing physician(s) were presumably the same & were not blinded to treatment allocation</p> <p>RCT with a high risk of bias</p> <p>SIGN evidence level 1-</p>
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Evidence table 3: finger/thumb osteoarthritis, health technology assessments & systematic reviews A – Z by author		
Study	Included relevant study	Outcomes, level of evidence etc.
<p>Health technology assessment (HTA) of prolotherapy for musculoskeletal pain; carried out for US Department of Veterans' Affairs (Adams 2008¹⁰)</p>	<p>One prospective, placebo-controlled double-blind RCT of dextrose prolotherapy for osteoarthritic thumb and finger joints (Reeves & Hassanein 2000²¹)</p>	<p>See evidence table for Adams HTA in back pain section, above.</p>

Study	Included relevant study	Outcomes, level of evidence etc.
Systematic review of prolotherapy for chronic musculoskeletal pain (Rabago et al 2005 ¹³)	One RCT, Reeves & Hassanein 2000 ²¹ as above	See evidence table for Rabago SR in back pain section, above.

Evidence table 4.1: knee osteoarthritis, health technology assessments & systematic reviews A – Z by author		
Study	Included relevant study	Outcomes, level of evidence etc.
Health technology assessment (HTA) of prolotherapy for musculoskeletal pain; carried out for US Department of Veterans’ Affairs (Adams 2008 ¹⁰)	One prospective, double-blind placebo-controlled RCT of dextrose prolotherapy for knee osteoarthritis with/without ACL laxity (Reeves & Hassanein 2000 ²²)	See evidence table for Adams HTA in back pain section, above.
Study	Included relevant study	Outcomes, level of evidence etc.
Systematic review of prolotherapy for chronic musculoskeletal pain (Rabago et al 2005 ¹³)	One RCT, Reeves & Hassanein 2000 ²² as above	See evidence table for Rabago SR in back pain section, above.

Evidence table 4.2: knee osteoarthritis (OA), RCTs A – Z by author				
Study	Inclusions	Interventions	Outcomes & results	Comments & level of evidence
Open label, randomised crossover study of regenerative injection therapy (RIT) in patients	Inclusion criteria: Patients aged 18+ with diagnosed knee OA & pain for ≥6 months; selected from a population of OA patients referred to an	Crossover design: All subjects assigned to 32 week home based exercise programme plus RIT on weeks 0, 4, 8 & 12 (Group A) or RIT on weeks 20, 24, 28 &	Outcomes assessed: Primary outcome: pain, joint stiffness & disability assessed on WOMAC index. Secondary outcomes: pain measured on Brief Pain Inventory, Wong-Baker “faces” scale & other pain scales (author also calculated a combined pain score); functional capacity assessed on timed up & go test Results:	9 patients (20%) lost to follow up; sample size underpowered for secondary outcomes RIT used here as adjunct to exercise programme; may confound attribution of improvements to RIT

<p>with chronic knee OA (Dumais et al 2012²³); carried out in New Brunswick, Canada</p>	<p>anaesthesiologist by an orthopaedic surgeon for pain management</p> <p>Included subjects:</p> <p>45 patients enrolled but only 36 (mean age approx 57 years, 19 (52.7%) male) completed the study</p>	<p>32 (Group B)</p> <p>RIT consisted of 1cc 15% dextrose solution injected into 8 admin sites in collateral ligaments plus one 5cc intra articular injection of 20% dextrose into knee joint</p>	<p>At 16 weeks, Group A showed significant reductions in symptoms measured on WOMAC index (mean $-21.8 \pm sd 12.5$, $p < 0.001$); the scores showed little change over the next 16 weeks when Group A received exercise therapy only (-1.2 ± 10.7, $p < 0.65$). Group B showed no significant change in WOMAC scores at 16 weeks (-6.1 ± 13.9, $p < 0.11$) but score reductions reached significance over the next 16 weeks when subjects received RIT in addition to exercise (-9.3 ± 11.4, $p < 0.006$). At 36 weeks, WOMAC scores improved by 47.3% in Group A versus 36.2% in Group B. Improvements in secondary outcomes were not as marked as for WOMAC scores</p> <p>Conclusions:</p> <p>RIT was associated with a marked reduction in symptoms, which was sustained for a further 24 weeks. The author argued that improvements due to RIT alone corresponded to a 11.9 point (29.5%), clinically important decrease in WOMAC scores</p>	<p>alone</p> <p>Author noted that (i) exercise programme may have contributed to Group A's maintained improvement in 2nd 16 week period; (ii) generalisability may be limited as subjects were relatively younger, heavier, more male & had more severe OA than typical OA populations</p> <p>This RCT had a high risk of bias: SIGN evidence level 1-</p>
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Study	Inclusions	Interventions	Outcomes & results	Comments & level of evidence
<p>Triple blind RCT of dextrose prolotherapy vs. control injections or exercise for knee OA (Rabago et al 2013²⁴)</p>	<p>Inclusion criteria:</p> <p>Subjects recruited from community & university clinics then observed for 1 year; inclusion criteria were clinical & radio-graphic OA diagnosis, tenderness on physical examination & moderate -severe knee pain for ≥ 3 months;</p>	<p>Intervention:</p> <p>Intra-articular injection of 6ml 25% dextrose solution plus up to 15 subdermal injections of 0.5ml 15% dextrose solution into ligament-bone insertions using "peppering technique"; injections were given to one or both knees at 1, 5 & 9 weeks; extra</p>	<p>Outcomes assessed:</p> <p>Primary outcome: composite WOMAC scores (assesses pain stiffness & function in OA). Secondary outcome: knee pain scale scores; tertiary outcomes: need for opioid pain medication, participant satisfaction. Outcomes assessed at weeks 5, 9, 12, 24 and 52</p> <p>Results:</p> <p><u>Primary outcomes:</u></p> <p>At 52 weeks, all three groups reported improved WOMAC scores compared to baseline ($p < .01$). Adjusted for age/sex/BMI, WOMAC scores at 52 weeks had improved more for the</p>	<p>Intention-to-treat analysis using analysis of variance was used; sample size was based on effect sizes seen in previous trials & clinical experience</p> <p>Authors noted that generalisability may be limited by exclusion criteria, relative youth of sample & lack of</p>

	<p>several exclusion criteria including daily opioid use</p> <p>Included subjects:</p> <p>90 subjects, 66% women, mean age 56.7 years, 74% overweight or obese, all had > 5 years of knee pain & had failed at least one conservative therapy; average OA severity was “moderate” on WOMAC</p>	<p>sessions were given at 13 & 17 weeks if requested by subject & recommended by physician</p> <p>Controls:</p> <p>Control (saline) injections administered as above or 20 week home-based exercise programme</p>	<p>prolotherapy group ($p < .05$) than had those for the saline & exercise groups (prolotherapy: 15.3 ± 3.5; saline: 7.6 ± 3.4; exercise: 8.2 ± 3.3); score changes exceeded the WOMAC-defined minimal clinically important difference.</p> <p>Improvements in the prolotherapy group reached a peak at 26 weeks and remained stable through to 52 weeks. Improvements were greatest for the function subscale of the WOMAC index</p> <p><u>Secondary outcomes:</u></p> <p>Knee pain scores improved more in the prolotherapy group ($p = .05$) & satisfaction with prolotherapy was high</p> <p>Conclusion:</p> <p>Prolotherapy resulted in clinically meaningful, sustained improvement of pain, function & stiffness scores for knee OA compared with blinded saline injections and home exercises</p>	<p>subjects with very severe baseline symptoms assessed on WOMAC</p> <p>This appears to be a well conducted RCT with low risk of bias: SIGN evidence level 1+</p>
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Evidence table 5.1: lateral epicondylitis - systematic reviews A – Z by author

Study	Inclusions	Interventions	Outcomes & results	Comments & evidence level						
<p>Systematic review & meta analysis of RCTs on corticosteroid & other injections for management of tendinopathies (Coombes et al 2010⁹)</p>	<p>Inclusion criteria: RCTs scoring >50% (i.e. at least 7/13) on a modified PEDro scale</p> <p>Included studies: 41 RCTs including one (Scarpone et al 2008²⁶, n=24, four subjects lost to follow up) on prolotherapy for chronic lateral epicondylosis. This RCT compared prolotherapy with 5% sodium morrhuate and 50% dextrose to saline injections. Injections were given at baseline and at 4 and 8 weeks. Outcomes were assessed at baseline, 8 and 16 weeks with long term follow up at 52 weeks.</p>	<p>Interventions: Peritendinous injections of corticosteroids or other agents</p> <p>Controls: Placebo or non-surgical interventions</p>	<p>Outcomes assessed: Primary outcome: protocol-defined pain score in the short, intermediate & long term. Other outcomes: function, patient satisfaction, adverse events</p> <p>Results: The reviewers gave the Scarpone RCT a PEDro score of 10 out of 13 (77%) and calculated the difference in overall pain reductions in the short and intermediate term as follows:</p> <table border="1" data-bbox="931 715 1816 901"> <thead> <tr> <th colspan="2" data-bbox="931 715 1816 762"><u>Pain reduction, standardised mean difference (95% confidence interval):</u></th> </tr> <tr> <th data-bbox="931 762 1377 798"><u>Short term</u></th> <th data-bbox="1377 762 1816 798"><u>Intermediate</u></th> </tr> </thead> <tbody> <tr> <td data-bbox="931 798 1377 901">0.27 (-0.61 to 1.15)</td> <td data-bbox="1377 798 1816 901">2.62 (1.36 to 3.88)</td> </tr> </tbody> </table> <p>No significant effects were seen in the short term, but a large reduction in pain was observed in the prolotherapy group ($p < 0.0001$) in the intermediate term (16 weeks)</p> <p>Adverse events: all subjects experienced temporary post-injection pain. Two subjects (20%) in the prolotherapy group experienced local irritation versus none in the control injection group: NNH (number needed to harm) = 5</p> <p>Conclusions: The authors suggested that prolotherapy injection of hypertonic glucose and local anaesthetic is a potential therapeutic technique, based on moderate evidence of improvements in the intermediate term for lateral epicondylalgia.</p>	<u>Pain reduction, standardised mean difference (95% confidence interval):</u>		<u>Short term</u>	<u>Intermediate</u>	0.27 (-0.61 to 1.15)	2.62 (1.36 to 3.88)	<p>This was a well conducted systematic review & meta-analysis with a low risk of bias as only high quality RCTs with a PEDro score of 7 or more were included: SIGN evidence level 1+</p> <p>However, the reviewers' conclusion regarding prolotherapy was based on the results of a single relatively small RCT, described by its authors as a pilot study</p>
<u>Pain reduction, standardised mean difference (95% confidence interval):</u>										
<u>Short term</u>	<u>Intermediate</u>									
0.27 (-0.61 to 1.15)	2.62 (1.36 to 3.88)									

Study	Inclusions	Interventions	Outcomes & results	Comments & level of evidence
<p>Systematic review & network meta-analysis of the comparative effectiveness and safety of injection therapies in lateral epicondylitis (Krogh et al, 2013²⁵)</p>	<p>Inclusion criteria: RCTs on adults with diagnosed lateral epicondylitis (i) comparing different injection therapies and (ii) containing data on change in pain intensity. RCTs involving participants with significant trauma or systemic inflammatory conditions were excluded</p> <p>Included studies: 17 RCTs involving 1381 participants & evaluating 8 different injection therapies. One RCT on prolotherapy (Scarpone et al²⁶, described above in evidence table for Coombes SR) was included</p>	<p>Interventions/controls: Any peri- or intra-tendinous injection vs. placebo injection or other active injection therapy</p>	<p>Outcomes assessed: Primary outcome: change in pain intensity (only the highest ranking pain measure in each study was extracted for the meta-analysis). Secondary outcome: safety & adverse events</p> <p>Results: Prolotherapy was more efficacious than placebo (saline) injection at 16 weeks: standardised mean difference -2.71 (95% confidence interval -4.60 to -0.82), p = .009. All subjects experienced self-limited post-injection pain & 2 in the prolotherapy group experienced transient local irritation 1 day post-injection</p> <p>The Scarpone RCT was considered to have an overall low risk of bias; however, the reviewers commented that it was small & its authors described it as a pilot study</p> <p>Conclusions: There is a paucity of evidence from unbiased trials on which to base treatment recommendations regarding injection therapies for lateral epicondylitis</p>	<p>Literature search failed to pick up RCT by Carayannopoulos et al⁴⁷ (2011), below</p> <p>This was a well conducted systematic review & meta-analysis with a low risk of bias: SIGN evidence level 1+</p>

Study	Inclusions	Interventions	Outcomes & results	Comments & evidence level			
<p>Systematic review of four injection therapies for lateral epicondylitis (Rabago et al²⁷, 2009)</p>	<p>Inclusion criteria: Studies of any design on the four injection therapies of interest, provided they reported pain outcomes pre- and post-treatment</p> <p>Included studies: Nine studies (n=208) of which three were RCTs (n=68)</p> <p><u>Prolotherapy studies:</u> Two RCTs: (i) Scarpone et al²⁶ (described above in evidence table for Coombes SR); (ii) 2006 pilot study by Glick²⁸: 8 subjects, mean age 50, randomised to 15% dextrose or saline injections at 0, 3 & 6 weeks, follow up at 9 weeks</p> <p>One prospective case series, Lyftogt 2007²⁹: 20 elbows (“refractory lateral elbow pain”) injected with 20% glucose using “<i>unconventional subcutaneous technique</i>”; injections given weekly for mean 7 weeks</p>	<p>Interventions: Prolotherapy, polidocanol, platelet-rich plasma or autologous blood injections</p> <p>Controls: As per primary study protocol (prolotherapy RCTs used saline injections)</p>	<p>Outcomes assessed: Clinical outcomes: the primary outcome of each study was pain assessed by visual analogue scale or questionnaire; the reviewers calculated several measures of effect size based (e.g. per cent improvement, Cohen’s d) on changes in pain scores published in the studies.</p> <p>Strength of evidence: quality of RCTs was assessed using Delphi internal validity criteria & all studies were given an overall quality score; an overall evidence grade (“strength of recommendation”) was also assigned to each therapy</p> <p>Results:</p> <table border="0"> <tr> <td data-bbox="943 715 1227 1018"> <p><u>Scarpone RCT</u>²⁶ Max improvement in pain with prolotherapy: 90% vs. 22% in controls (p<0.001) at 6 weeks. Cohen’s d=6.68. Prolotherapy subjects “qualitatively reported maintenance of treatment effects at 12 months”. Delphi score 8/9</p> </td> <td data-bbox="1240 715 1509 959"> <p><u>Glick RCT</u>²⁸ Max improvement on disease-specific questionnaire with prolotherapy: 66% vs. 11.5% in controls (p=0.09) at 9 weeks. Cohen’s d=1.6. Delphi score 7/9</p> </td> <td data-bbox="1541 715 1794 847"> <p><u>Lyftogt case series</u>²⁹ 94% improvement compared with baseline scores (p<0.05)</p> </td> </tr> </table> <p>Conclusions: There is strong (in terms of effect sizes) pilot-level evidence supporting the use of prolotherapy (SORT grade 1B) & the other three injection therapies for the treatment of lateral epicondylitis. All included studies had small samples and other limitations & none of the four therapies can be recommended over the others. Prolotherapy is the cheapest/easiest of the four to implement.</p>	<p><u>Scarpone RCT</u>²⁶ Max improvement in pain with prolotherapy: 90% vs. 22% in controls (p<0.001) at 6 weeks. Cohen’s d=6.68. Prolotherapy subjects “qualitatively reported maintenance of treatment effects at 12 months”. Delphi score 8/9</p>	<p><u>Glick RCT</u>²⁸ Max improvement on disease-specific questionnaire with prolotherapy: 66% vs. 11.5% in controls (p=0.09) at 9 weeks. Cohen’s d=1.6. Delphi score 7/9</p>	<p><u>Lyftogt case series</u>²⁹ 94% improvement compared with baseline scores (p<0.05)</p>	<p>The DARE commentary on this review notes “<i>The validity of all studies was not assessed & results were reported as aggregate scores...Incomplete reporting of study quality & small sample sizes mean that the reviewers’ conclusions, although cautious, may not be reliable</i>”³⁰</p> <p>ACC is unable to trace a copy of the Glick RCT</p> <p>This was a reasonably conducted systematic review with some risk of bias: SIGN evidence level 1+/1-</p>
<p><u>Scarpone RCT</u>²⁶ Max improvement in pain with prolotherapy: 90% vs. 22% in controls (p<0.001) at 6 weeks. Cohen’s d=6.68. Prolotherapy subjects “qualitatively reported maintenance of treatment effects at 12 months”. Delphi score 8/9</p>	<p><u>Glick RCT</u>²⁸ Max improvement on disease-specific questionnaire with prolotherapy: 66% vs. 11.5% in controls (p=0.09) at 9 weeks. Cohen’s d=1.6. Delphi score 7/9</p>	<p><u>Lyftogt case series</u>²⁹ 94% improvement compared with baseline scores (p<0.05)</p>					

Evidence table 5.2: lateral epicondylitis – RCTs A – Z by author

Study	Inclusions	Interventions	Outcomes & results	Comments & level of evidence
<p>Randomised double blind trial of prolotherapy for lateral epicondylosis (Carayannopoulos et al 2011⁴⁷); carried out in a university hospital outpatient rehab clinic in the US</p>	<p>Inclusion criteria: People with clinically determined lateral epicondylosis lasting 3 months-2 years recruited via ads in tennis clubs & direct physician referral</p> <p>Included subjects: 24 subjects enrolled, only 17 completed the study (mean age 46, 65% female)</p>	<p>Intervention: Prolotherapy with 1.2% phenol, 12.5% glycerine, 12.5% dextrose</p> <p>Control: Corticosteroid injection</p> <p>Two injections given (baseline & 1 month)</p>	<p>Outcomes assessed: Pain rated on visual analogue scale (VAS) & quadruple visual analogue scale (QVAS); symptoms & functional status rated on disabilities of the arm, shoulder & hand (DASH) questionnaire; grip strength & maximum grip. Outcomes assessed at baseline and at 1, 3 and 6 month follow up</p> <p>Results: Both groups reported improvements over the course of the study, but there were no significant differences between the groups. Improvements tended to be maintained in the prolotherapy group</p> <p>Conclusions: Prolotherapy may be a useful alternative to corticosteroid injection; larger studies are required.</p>	<p>Underpowered RCT: authors aimed to recruit 56 subjects but only enrolled 24 & only 17 actually completed the study</p> <p>No. of injections was limited to allow comparison with standard corticosteroid regime</p> <p>RCT with a high risk of bias: SIGN evidence level 1-</p>

Study	Inclusions	Interventions	Outcomes & results	Comments & evidence level
<p>Pilot level RCT of two prolotherapy solutions for lateral epicondylitis (Rabago et al 2013³¹);</p>	<p>Inclusion criteria: Patients aged 18-65 with lateral elbow pain for ≥ 3 months & self-rated pain level ≥ 4 on a 0-10 scale recruited from community & university rehab clinics; must have failed ≥ 1 of 3 most common tennis elbow treatments (corticosteroid injection, NSAIDS, physical therapy); lateral epicondylitis confirmed by physical examination prior to enrolment</p> <p>Included subjects: 27 subjects (32 affected elbows), 65% male, mean age 48.2 years, mean elbow pain duration ≥ 3 years</p>	<p>Interventions: Blinded allocation to ultrasound-guided injections at 1, 4 & 8 weeks of 50% dextrose (n=8, 10 elbows) OR 50% dextrose plus 5% sodium morrhuate (n=9, 10 elbows)</p> <p>Control: Watchful waiting plus counselling on risk modification in work & daily life (n=10, 12 elbows)</p>	<p>Outcomes assessed: Primary: Patient Rated Tennis Elbow Evaluation (PRTEE) scores at 4, 8 & 16 weeks (all) and 32 weeks (prolotherapy groups). Secondary: grip strength, MRI evaluation of symptom severity at 16 (all) and 32 weeks (prolotherapy groups). Tertiary outcome: treatment satisfaction rating.</p> <p>Results: Dextrose participants: improvements vs. baseline in PRTEE composite & pain (at 16 & 32 weeks) and function (at 32 weeks) scores; dextrose-morrhuate participants: improvements vs. baseline in composite (at 32 weeks), pain (at 16 & 32 weeks) and function (at 32 weeks) scores. Improvements in both prolotherapy groups were statistically significant vs. baseline & wait group. PRTEE composite score improvements at 16 weeks exceeded the minimal clinically important differenceⁱⁱ.</p> <p>At 16 weeks, age-adjusted composite scores in the dextrose & dextrose-morrhuate groups had improved by a mean 18.7 SE 9.6 (41%) and 17.5 SE 11.6 (53.5%) points respectively vs. 9.3 SE 11 (11%) in the wait group.</p> <p>Improvements were maintained in both prolotherapy groups at 32 weeks. Dextrose participants appeared to improve more quickly & experienced less post-injection pain than dextrose-morrhuate participants.</p> <p>Grip strength of dextrose participants exceeded that of dextrose-morrhuate & wait participants at 8 and 16 wks ($p > 0.05$). There were no differences in MRI scores. Satisfaction with prolotherapy was high; no adverse events apart from injection pain (more severe/persistent with dextrose-morrhuate).</p> <p>Conclusions: Both prolotherapy solutions gave safe, significant improvement of pain & function compared with baseline status and a wait-and-see control group.</p>	<p>Relatively small sample size, but in line with the authors' a priori calculation of 30 (10 per group), based on expected effect sizes</p> <p>Dextrose-morrhuate group slightly younger than other two groups ($p=0.047$)</p> <p>Assessor & injector not blinded to injection type</p> <p>Reasonably well designed pilot-level RCT with low risk of bias: SIGN evidence level 1+</p>

ⁱⁱ 11 points or 37% improvement compared with baseline.

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