A systematic review of prolotherapy for chronic musculoskeletal pain
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CRD summary
This review assessed the effectiveness of prolotherapy for the treatment of chronic musculoskeletal pain. The authors concluded that few high-quality studies support the use of prolotherapy and that further research is required. The limited and conflicting evidence from a few high-quality studies was adequately reflected in the authors' conclusions.

Authors' objectives
To assess the effectiveness of prolotherapy (PrT) for the treatment of chronic musculoskeletal pain and soft tissue injury.

Searching
MEDLINE, EMBASE, CINAHL and AMED were searched from inception to 2004, using the reported search terms, for articles published in any language. The reference lists of identified studies were screened and experts in the field were contacted.

Study selection
Study designs of evaluations included in the review
Studies of any design were eligible for inclusion. The review included RCTs, non-randomised controlled trials, case series and case reports. The included RCTs followed up patients for between 6 and 24 months.

Specific interventions included in the review
Studies of PrT were eligible for inclusion. The included studies used a variety of protocols for administration: PrT was generally given with dextrose with and without lidocaine or phenol-glucose-glycerine. The comparison interventions, where these existed, included injections of lidocaine alone, saline, saline/lidocaine and bacteriostatic water/lidocaine and conservative therapies. In some studies injected steroids, spinal manipulation and exercise were given before PrT.

Participants included in the review
The review focused on patients with any type of chronic musculoskeletal pain or soft tissue injury. The included studies were in children and adults (aged 12 to 88 years), most of whom had (undifferentiated) low back pain, sacroiliac dysfunction or osteoarthritis (including metacarpal and knee osteoarthritis). The mean duration of pain in randomised controlled trials (RCTs) ranged from 4.5 to 14 years.

Outcomes assessed in the review
Inclusion criteria were not defined in terms of the outcomes. The review assessed response rates as defined by the studies (including the percentage of patients with >50% improvement in pain or disability scores), subjective pain (including leg and low back pain), disability, movement, flexion of joints and hand-grip.

How were decisions on the relevance of primary studies made?
The authors did not state how the studies were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
RCTs were assessed using the Jadad and Delphi scoring systems. Three unblinded reviewers assessed the quality of each RCT and any disagreements were resolved by consensus. The authors did not state that they assessed the validity of studies with other designs.

Data extraction
One reviewer extracted the data from case reports, case series and non-randomised controlled trials; it was unclear how many reviewers extracted the data from RCTs. The data extracted from each study varied and included results reported as text and values for outcomes of interest, with and without the level of statistical significance.

**Methods of synthesis**

How were the studies combined?
The studies were grouped by study design and combined in a narrative.

How were differences between studies investigated?
RCTs in patients with osteoarthritis and low back pain were discussed separately. Some differences between the studies were discussed in the text, whilst others were apparent from the tables.

**Results of the review**

Six RCTs (439 adults) and 34 case reports, case series and non-randomised controlled trials (3,831 children and adults) were included.

**RCTs.**

The RCTs were of a high quality, scoring 4 or 5 out of 5 on the Jadad scale and 7 to 9 out of 9 on the Delphi internal validity assessment.

Osteoarthritis: 2 RCTs were identified. One study found that PrT (with dextrose plus lidocaine) significantly improved finger movement (p=0.027) and the range of finger flexion (p=0.003) compared with lidocaine plus bacteriostatic water, but found no significant difference between treatments for pain at rest or grip. The other study of knee osteoarthritis found that both treatments significantly improved pain scores, swelling, buckling episodes and flexion compared with baseline.

Low back pain (4 RCTs): the results were mixed. Two RCTs found PrT preceded by injected steroids, manipulation and exercise significantly increased the proportion of patients with >50% improvement compared with control (88% versus 39% with pain reduction, p<0.031 and 77% versus 53% with reduction in pain score or disability, p=0.04). The other 2 RCTs found no significant difference between PrT alone and control in pain or somatic perception scores (1 RCT) or between a non-standard PrT injection protocol and control in pain and disability (the largest and highest quality RCT).

Adverse effects (6 RCTs): the studies suggested that PrT (as used in the included studies) was associated with short-term pain and irritation at the injection site.

Case reports, case series and non-randomised controlled trials (34 studies).

Taken all together, the studies reported positive subjective outcomes with few adverse effects.

Two non-randomised controlled trials reported positive effects with PrT in low back pain. One found PrT non statistically significantly improved response rate compared with control. The other found significant improvements in pain and leg pain and non significantly decreased disability and back pain compared with conservative treatment.

**Authors’ conclusions**
The limited number of high-quality studies precluded drawing firm conclusions about PrT. Further research is required.

**CRD commentary**
The review question was clearly but broadly defined in terms of the intervention, study design and participants; inclusion criteria for the outcomes were not specified. Several relevant sources were searched and attempts were made to minimise language bias. It was unclear whether or not unpublished studies were eligible, so it was not possible to
assess the potential for publication bias. Methods were used to minimise reviewer errors and bias in the assessment of
the validity of RCTs, but other parts of the review process were either not described or were performed by a single
reviewer. This lack of duplication might have led to reviewer errors and bias, whilst the lack of information on review
methodology meant that the potential for reviewer error and bias could not be assessed. The quality of the RCTs was
assessed using an aggregated quality scoring system but details of the individual components were not consistently
reported. There were no details of criteria used to assess the quality of other studies.

The studies were appropriately grouped by study design and combined in a narrative. Some potential causes of
differences between the studies were discussed. There were limitations to this review, such as the incomplete reporting
of review methodology. The limited and conflicting evidence from a few high-quality studies was adequately reflected
in the authors' conclusions.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that there is a need for further adequately powered, high-quality RCTs of sports-related
and musculoskeletal conditions that compare prolotherapy with a noninjection control and select participants based on
physical examination. The authors also stated there is a need to determine the mechanisms underlying the action of PrT
injections.

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