PROLOTHERAPY

HEALTH TECHNOLOGY ASSESSMENT SECTION

MEDICAL DEVELOPMENT DIVISION

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EXECUTIVE SUMMARY

Introduction

Musculoskeletal conditions are prevalent and their impact is pervasive due to the frequency, chronicity and resultant disability. Prolotherapy is an injection-based treatment for chronic musculoskeletal pain, with a volume of proliferant solution is injected at sites of painful tendon and insertions, and in adjacent joint space in a number of treatment sessions. The purpose is to strengthen weakened connective tissue and alleviate musculoskeletal pain. Areas that are most likely to benefit are ankles, knees, elbows and the sacroiliac joint located at the lower back. Its most common application in the back is chronic non-specific low-back pain that has not responded to other therapies. This review was requested by Head of Health Technology Assessment Section, Ministry of Health following an inquiry from an insurance company.

Aims/objectives

To assess the safety, effectiveness, cost effectiveness and organisational aspect of prolotherapy for the treatment in musculoskeletal disorders.

Results and conclusion

Based on the review, in terms of efficacy, there was evidence to show that prolotherapy injection yielded good clinical response and likely to be effective in several tendinopathies; in particular improvement in pain scores and strength testing in lateral epicondylosis. It can also improve pain score and sonographical parameters in Achilles tendinopathy. For chronic non-specific low back pain, evidence showed that prolotherapy is not an effective treatment when used alone. However it may improve chronic low back pain when combined with spinal manipulation, exercise, and other co-intervention. For osteoarthritis of the peripheral joints, evidence showed that prolotherapy may have a role in the improvement of pain with joint movement and range limitation in osteoarthritic finger and knee joint. With regards to safety aspect, evidence showed that side effects related to prolotherapy for back pain was temporary and benign, and no serious adverse events were reported for prolotherapy when used for peripheral joint indications.

Methods

Literature were searched through electronic databases which included PubMed, Medline and Cochrane Database via Ovid search engine and general databases such as Google and Yahoo.
The search strategy used the terms, which were either used singly or in various combinations: “prolotherapy”, “prolotherapy injection”, “proliferant”, “musculoskeletal disorders”, “musculoskeletal condition”, “low back pain”, “tendinopathies” and “treatment”. The search was limited to articles on human. There was no language limitation in the search.

Systematic reviews, meta-analysis and randomised clinical trials pertaining to effectiveness, safety and cost effectiveness of isokinetic exercise machine were included.

A critical appraisal of all relevant literature was performed using Critical Appraisal Skills Programme (CASP) checklists and the evidence graded according to the US/Canadian Preventive Services Task Force Level of Evidence (2001).

PROLOTHERAPY

1. INTRODUCTION

Musculoskeletal conditions are prevalent and their impact is pervasive due to the frequency, chronicity and resultant disability. The burden has been recognized by the United Nations and WHO by endorsing the Bone and Joint Decade 2000-2010. They encompass a spectrum of condition from acute onset to lifelong disorders, including osteoarthritis and low back pain. Osteoarthritis, which is characterized by loss of joint cartilage leads to pain and loss of function primarily in the hip and knee, affects 9.6% men and 18.0% women above 60 years worldwide. Increases in life expectancy and ageing populations are expected to make musculoskeletal conditions particularly osteoarthritis among the leading cause of disability. Low back pain is the most prevalent of musculoskeletal conditions, affecting nearly everyone at some point in time and approximately 4-33% of the population at any given point. Frequently, episodes of low back pain never fully resolve. Lifetime recurrence can rise up to 85%.[1]

Prolotherapy is an injection-based complementary and alternative treatment for chronic musculoskeletal pain. Historically, as early as late 1800s, injections of irritant solutions were initiated to repair hernias and to treat jaw pain due to temporomandibular joint laxity in early 1900s. Its modern application is said to be formalized by George S. Hackett, a surgeon in the US in the 1950s. Interest in prolotherapy among patient and physician is high, and it is increasingly popular internationally. While prolotherapy techniques and injected solution vary by condition, clinical severity and practitioner preferences, a basic principle is that a volume of proliferant solution is injected at sites on painful tendon and insertions, and in adjacent joint space over the treatment sessions. Prolotherapy has been used to treat chronic low back pain for over 50 years however their use still remains controversial.[2]

This review was requested by Head of Health Technology Assessment Section following a query by a Claims Specialist of an insurance company (Prudential Assurance Malaysia Berhad).

2. OBJECTIVES

To assess the safety, effectiveness, cost effectiveness and organisational aspect of prolotherapy for the treatment of musculoskeletal disorders.

3. TECHNICAL FEATURES

Prolotherapy is an injection-based treatment for chronic musculoskeletal pain. The term prolotherapy comes from the word *prolix* (Latin), which means offspring or proliferate-to produce new cells in rapid succession. It is a method of treating chronic ligament and tendon weakness, where the weakened areas are repeatedly injected with a proliferant solution to help restart body's natural healing process by causing controlled acute inflammation. As the

tendons and ligaments grow stronger and healthier, the pain is alleviated. The purpose is to strengthen weakened connective tissue and alleviate musculoskeletal pain.[3,4] Proliferants (injected solutions) have historically been hypothesized to cause local irritation, with subsequent inflammation and tissue healing, resulting in strengthening of damaged ligamentous, tendon and intra-articular structures. These processes were thought to improve joint stability, biomechanics, function and eventually to reduce pain.[2]

It is also known as "sclerotheraphy", "proliferation therapy", "proliferative injection therapy", "regenerative injection therapy" or "ligament sclerotherapy". The healing process is expected to take about six weeks after the initial treatment. [3,4]

Protocols for prolotherapy varies, but generally consists of several injection sessions delivered every 2 to 6 weeks over the course of several months, with less frequent interval until it is required only every several years.[2,3,4] Prolotheraphy protocols for back pain also varies, but all include the injection of proliferant solution into ligaments and tendinous attachments at weekly or fortnightly intervals for 3 to 8 treatments.[6]

Areas that are most likely to benefit from prolotherapy treatment are ankles, knees, elbows and the sacroiliac joint located at the lower back. Its most common application in the back is chronic non-specific low-back pain that has not responded to other therapies.[3,4]

Figure : Different type of proliferants used (left)
and process of injecting proliferants to knee (right).

The characteristic of wound healing process involve activation of wound healing cascade, which include three critical phases; an initial inflammatory reaction which attracts other important cells to the injury site; a secondary inflammatory response in which macrophages secrete humoral factors which attract fibroblasts; finally an infiltration and activation of fibroblasts which lay down new collagen, giving strength to the injury site.[5]

Mechanism of action of prolotherapy is injection of proliferant which will initiate local inflammation or the first phase of wound healing cascade. The inflammation launches a wound healing cascade where it triggers an influx of granulocytes, macrophages and fibroblasts which will be attracted to the injection site, and the release of growth factors resulting in the deposition of new collagen and a hypertrophied ligament. New collagen loses volume and contracts as it matures. The new collagen that is produced at the injection site undergoes contraction and pulls the ligament tighter, eventually strengthen the ligaments and reduce pain and disability. The hypertrophied ligament is more robust and tighter due to the contraction which occurs with recently deposited collagen. These processes were thought to improve joint stability, biomechanics, function and ultimately to reduce pain.[5]

Proliferant solutions vary in the mechanism by which they cause localized inflammation but, in general, they all act by causing localized tissue trauma or irritation which initiates an influx of inflammatory cells. The exception to this rule is sodium morrhuate which may act as a chemotactic factor by a more direct mechanism.

There are three major classes of proliferants commonly used in prolotherapy -- the irritants, the chemotactics and the osmotic.[5] There is some over-lap in their purported actions.

i. Irritants

The first class of proliferant solutions, called irritants or haptens act by either damaging cells directly or by rendering the cells antigenic through alteration of surface proteins. Irritants include phenol, guaiacol, tannic acid and phenol-glycerine-glucose. There is another category of irritants called particulates, exemplified by pumice flour. These act by triggering cellular trauma following injection into target tissues, and by directly attracting macrophages, which ingest them and secrete polypeptide growth factors. In either case, granulocytes and macrophages are attracted to the injection site and early inflammation occurs; in other words, the wound healing cascade is initiated.

ii. Chemotactics

A second class of proliferants only has one member currently; sodium morrhuate that contains the biosynthetic precursor to certain chemotactic agents which attract inflammatory cells. Sodium morrhuate is the sodium salt of the fatty acid component derived from cod liver oil. These compounds are direct biosynthetic precursors to the mediators of inflammation such as prostaglandins, leukotrienes and thromboxanes. [5]

iii. Osmotics

A third class of proliferant is osmotics proliferants which includes concentrated/hypertonic solutions of glucose, glycerin and zinc sulphate. These agents act by dehydrating cells at the injection site; where it causes an osmotic shock to cells leading to the release of pro-inflammatory substances. Cells at the injection site, which are either morbid or dead, release cellular fragments (proteins, membrane fragments and the like) which are attractive for granulocytes and macrophages. Thus, local tissue damage causes an influx of inflammatory cells and initiates the wound healing cascade. [5]

Local anaesthetic (commonly lignocaine) is often added to proliferant solutions to reduce the pain of the irritant injections. [3,4]

4. METHODOLOGY

4.1 SEARCH METHODS

Literature were searched through electronic databases which included PubMed, Medline and Cochrane Database via Ovid search engine, and general databases such as Google and Yahoo. The search strategy used the terms, which were either used singly or in various

combinations: “prolotherapy”, “prolotherapy injection”, “proliferant”, “musculoskeletal disorders”, “musculoskeletal condition”, “low back pain”, “tendinopathies” and “treatment”. The search was limited to articles on human. There was no language limitation in the search.

4.2 SELECTION OF STUDIES INCLUDED /EXCLUDED

Systematic reviews, meta-analysis and randomised clinical trials pertaining to effectiveness, safety, and cost effectiveness of prolotherapy conducted in human with musculoskeletal pain were included.

A critical appraisal of all relevant literature was performed using Critical Appraisal Skills Programme (CASP) checklists and the evidence graded according to the US/Canadian Preventive Services Task Force Level of Evidence (2001).

Data were extracted and summarized in evidence table as in Appendix 3. The data were not pooled and only qualitative analysis was carried out.

5. RESULTS AND DISCUSSION

There were eight articles on prolotherapy retrieved. Two of the articles were systematic review, the other three were randomized controlled trials, and one article each was on cohort study, case series and cross sectional studies.

5.1 EFFICACY/EFFECTIVENESS

Simon Dagenais *et al*. conducted a systematic review which included five primary studies (Dechow, Klein, Mathews, Ongley, Yelland) that examined the effects of prolotherapy injections on 366 adult patients with low back pain that had lasted for longer than 3 months. He included randomised (RCT) and quasi-randomised controlled trials (QRCT) that compared prolotherapy injections to control injections, alone or in combination with other treatments, which measure pain and disability before and after the intervention. Prolotherapy injection had to be administered to at least one group within trial, and control group receive control solution or different therapy not involving injection. All the five studies included measured pain and disability level at 6 months, and four measured proportion of participants reporting greater than 50% reduction in pain and disability scores. He found that in 3 RCTs (n=206), prolotherapy injections alone are not an effective treatment for chronic low back pain, and disability. At 6 months, there was no difference between groups in mean pain or disability scores (2 RCTs; n=184), and no difference in proportions who reported over 50% improvement in pain or disability (3 RCTs; n=206). He also found that prolotherapy injection, given with spinal manipulation, exercise and other therapies are more effective than control injections for chronic low back pain and disability (2 RCTs; n=180). The author concluded that when used alone, prolotherapy is not an effective treatment for chronic low back pain. When combined with spinal manipulation, exercise, and other co-intervention, prolotherapy may improve chronic low back pain.[6 level I]

Chou *et al*. conducted a systematic review to assess benefits and harms of nonsurgical intervention therapies for low back and radicular pain. Prolotherapy was included as one of the interventional therapies in his review, apart from botulinum toxin injection, epidural steroid injection, facet joint injection, therapeutic medial branch block, chemonucleolysis, radiofrequency denervation and others. The systematic review by Degenais is cited as the only evidence in his review with regards to effectiveness of prolotherapy in comparison to other intervention. The author concluded that there is fair evidence that prolotherapy, facet joint injection, intradiscal steroid injection and percutaneous intradiscal radiofrequency thermocoagulation are ineffective in nonspecific low back pain. [7 level I]

Khan *et al.* in a prospective longitudinal study assessed 37 subjects with coccyygodynia to determine effectiveness of dextrose prolotherapy in chronic coccygodynia not responding to conservative treatment for more than 6 months. Subjects received 25% dextrose injection and 2 ml 2% lignocaine into the coccyx, in up to 3 injection sessions over 2 months; at baseline, day 15, and 4 weeks later for patient with Visual Analogue Scale (VAS) score above 4. They found that mean VAS score decreased from 8.5 before intervention to 3.4 (after first injection) and further reduce to 2.5 (after second injection). The author concluded that prolotherapy was effective in non-responding, obstinate coccygeal pain and recommended prolotherapy before resorting to coccygectomy in these subjects in view of possibly high complication rates.[8 level II-2]

A pre-assessment on prolotherapy for the treatment of chronic musculoskeletal pain conducted in 2004 by the Canadian Coordinating Office for Health Technology Assessment revealed that there is little point to undertake further assessment of it at that particular time though further evidences are needed from controlled clinical trials.[9] Technology assessment conducted by Feldman. in 2004 for prolotherapy in the treatment of chronic low back pain revealed that the evidence on whether prolotherapy is superior to placebo for the treatment of chronic low back pain is inconclusive.[10] In a 2009 guideline by NICE on low back pain: early management of persistent of non specific low back pain, they do not recommend injections of therapeutic substances into the back for non-specific low back pain.[11]

Reeves and Hassanein assessed prolotherapy as a treatment for osteoarthritis (OA). He conducted a randomised prospective double blind placebo controlled study of dextrose prolotherapy for knee OA with or without knee laxity. He included 68 subjects with 111 knees with knee pain for six months and more, and radiographic evidences of OA which is either grade 2 or more osteophytic change in any knee compartment, whom underwent 3 bimonthly injections of prolotherapy with 10% dextrose and lidocaine, versus an identical control solution. The study demonstrated a statistically superior effect of active solution (dextrose); with significant improvement in pain (at rest, with walking, with stair use) and swelling score, number of buckling episodes, and flexion range at 6 months compared to baseline ($p=0.015$). The study also showed statistically significant improvement in radiographic features (increase patellofemoral thickness and distal femur width) for the dextrose treated knees between 0 to 12 months. He concluded that prolotherapy with dextrose injection is clinically and statistically superior to control solution (bacteriostatic water) in treatment of OA of the knee.[12 level I]

Similarly, Reeves and Hassanein also assessed prolotherapy as a treatment for osteoarthritis (OA) of fingers, where he conducted a randomised placebo controlled, double blind study of dextrose prolotherapy for osteoarthritic thumb and finger (DIP, PIP and trapeziometacarpal) joints, to determine the clinical benefit of dextrose prolotherapy in osteoarthritic finger joints. He included subjects with 6 months of pain history in each joint with one of the radiologic changes of OA (either grade 2 or 3 osteophyte, grade 2 or 3 joint narrowing, or grade 1 osteophyte plus grade 1 joint narrowing), whom received injections of 0.5 ml either 10% dextrose and xylocaine in bacteriostatic water (active solution) or identical control solution. Subjects included were 13 patients receiving active treatments, and 14 patients as controls (each with 74 and 76 symptomatic OA joints respectively). Visual Analogue Scale (VAS) score for pain with movement is statistically significant in the treated group ($p=0.027$). There is significant improvement in goniometrically measured joint flexion; with flexion range of motion in dextrose treated joints (+8 degrees) than the placebo treated joints (-8.6 degrees) ($p=0.027$). The study also showed statistically significant improvement in radiographic features (decreased joint space narrowing and osteophyte grade) for the dextrose treated knees between 0 to 12 months. It is concluded that dextrose prolotherapy is effective and safe in the treatment of pain with joint movement and range limitation in osteoarthritic finger joints.[13 level I]

In another double blind randomised controlled trial, Scarpone *et al.* assessed the efficacy of prolotherapy for lateral epicondylosis (tennis elbow) in terms of improvement in elbow pain, grip strength and extension strength. This study included 24 adult patients with at least 6 months of refractory lateral epicondylosis. The intervention group received prolotherapy injections with dextrose and sodium morrhuate (1 part 5% sodium morrhuate, 1.5 parts 50% dextrose, 0.5 parts 4% lidocaine, 0.5 parts 0.5% sensorcaine and 3.5 parts normal saline) while the control received injection with normal saline, with injection administered at baseline, 4 and 8 weeks. They found that prolotherapy subjects had improvement in resting elbow pain scores (4.5 ± 1.7, 3.6 ± 1.2, 3.5 ± 1.5, versus 5.1 ± 0.8, $3.3. \pm 0.9$ and 0.5 ± 0.4) compared to controls at baseline, 8 and 16 weeks respectively. At 16 weeks the difference was significant ($p<0.001$). Prolotherapy subjects also showed significant improvement in extension strength at 8 and 16 weeks, compared to baseline score ($p<0.01$) and controls ($p<0.01$); and grip strength compared to baseline score ($p<0.05$). He concluded that prolotherapy with dextrose and sodium morrhuate is effective in decreasing elbow pain and improving strength testing in refractory lateral epicondylosis.[14 level I]

Maxwell *et al.* assessed effectiveness of hyperosmolar (25%) dextrose injection into hypoechoic region of Achilles tendon under ultrasound guidance. This study included 36 adults with painful Achilles tendinopathy with symptoms more than 3 months. Mean of 4 injection sessions (range 2-11) at every 6 weeks interval were given. At baseline and before each injection, clinical assessment was performed using Visual Analogue Score (VAS) for pain at rest, during normal daily activity, and during or after physical activity or sport; and sonographic parameters including tendon thickness, echogenicity and neovascularity were recorded. They found that at 52 weeks, there was a significant improvement in pain score, with mean percentage reduction in pain of 88%, 84% and 78% during rest, with daily activity and sport respectively ($p<0.0001$). They also found significant reduction in mean tendon

thickness from 11.7 to 11.1mm ($p<0.007$) sonographically. The author concluded that intratendinous injection of hyperosmolar dextrose yielded a good clinical response in patient with Achilles tendinopathy. [15 level III]

5.2 SAFETY

The systematic review by Dagenais *et al.* reported that nearly all patients in most trials experience temporary increase in back pain and stiffness following prolotherapy injections. Post injection headaches occurred in 2-4% of patients in trials by Klein and Yelland.[6 level I] Scarpone *et al.* reported minimal side effects of injection therapy using sodium morrhuate in all subjects (n=20), in which all experienced self limited post injection pain, with two experienced one episode each for local erythema, irritation and discomfort for approximately one day post injection. He reported no allergy reaction to sodium morrhuate.[14 level I]

Degenais *et al.* conducted a postal survey on side effects and adverse events related to intraligamentous injection of sclerosing solution (prolotherapy) for back and neck pain to 171 practicing prolotherapist in United States and Canada. They found that side effects with highest median estimated prevalence were pain (70%), stiffness (25%) and bruising (5%), with a total of 472 adverse events being reported including 69 that requires hospitalization and 5 resulted in permanent injury due to nerve injury. The author concluded that side effects related to prolotherapy for back and neck pain such as temporary postinjection pain, stiffness and bruising are common and benign. No serious adverse events were reported for prolotherapy when used for peripheral joint indications.[16 level III]

Dextrose, the commonest proliferant used is safe and approved by FDA for intravenous treatment of hypoglycaemia and for caloric supplementation. Morrhuate sodium, another proliferant is a vascular sclerosant used in gastrointestinal procedure and vein sclerosing. Allergic reactions to sodium morrhuate is rare. Phenol-glycerine-glucose (P2G), another type of proliferant is not FDA approved.[17]

5.3 COST EFFECTIVENESS

There was no article retrieved on cost effectiveness of prolotherapy. However, the cost per injection is around [redacted]

5.4 ORGANISATIONAL ASPECT

5.4.1 TRAINING

There was no study retrieved on training aspect requirement of operators prior practicing the procedure. Prolotherapy is an operator dependant procedure and unregulated without certification by any governing body. Formal training is currently not provided by most medical schools or fellowships. However, prolotherapy, to be practiced and performed safely on patients, requires specialized individual training.[2 level III]

6. CONCLUSION

Based on the review, in terms of efficacy, there was evidence to show that prolotherapy injection yielded good clinical response and likely to be effective in several tendinopathies; in particular improvement in pain scores and strength testing in lateral epicondylosis, and improvement in pain score and sonographical parameters in Achilles tendinopathy. For chronic non specific low back pain, evidence showed that prolotherapy is not an effective treatment when used alone. However, it may improve chronic low back pain when combined with spinal manipulation, exercise, and other co-intervention. For osteoarthritis of the peripheral joints, evidence showed that prolotherapy may have a role in the improvement of pain with joint movement and range limitation in osteoarthritic finger and knee joint. With regards to safety, evidence showed that side effects related to prolotherapy for back pain was temporary and benign such as postinjection pain, stiffness and bruising. No serious adverse events were reported for prolotherapy when used for peripheral joint indications. However, there were reports of nerve injury when using prolotherapy for back and neck pain.

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