7.11 Prolotherapy

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Introduction

Prolotherapy is an injection therapy used to treat chronic ligament, joint, capsule, fascial, and tendinous injuries. The goal of this treatment is to stimulate proliferation of collagen at the fibro-osseous junctions to promote nonsurgical soft tissue repair and to relieve pain (see Fig 7.11.1) (Klein & Eck 1997). Originally defined by Hackett as "the rehabilitation of an incompetent structure (ligament or tendon) by the generation of new cellular tissue", it has received a variety of names (Dagenais et al. 2005; Alderman 2007).

It now includes all regenerative methods by injection including dextrose-based, inflammation-based, platelet-rich plasma, (adult) stem cell-based, and essentially any other injection method in which either growth factors are stimulated or disrepair factors are blocked.

Growth factors are powerful polypeptides that induce wide-ranging effects including cell migration, proliferation, and protein synthesis. These proteins may be produced by the affected cells or in other cells. These growth factors must avoid the binding proteins which could cause their inactivation, find their way to the area needing growth, and hook onto an appropriate receptor protein (Reeves 2000).

Prolotherapy has been used extensively in the USA since the 1930s (over 450 000 people have undergone prolotherapy treatment) and in other countries around the world. Yet it has not become a mainstream therapy (Mooney 2003). The abundance of case series studies and anecdotal evidence has not been supported by a large body of randomized controlled trials (Yelland et al. 2003; Dagenais et al. 2007).

History

Hippocrates (*trans* by Francis Adams 1946) (460–370 BCE) was the first to describe the intentional provocation of scar tissue formation by searing the shoulder capsules in the unstable shoulders of javelin throwers in Sparta. Two millennia later, in 1837, Robert Valpeau of Paris described the use of scar formation for the repair of hernias. One hundred years later, Yeomans (1939) extensively reviewed the genealogy of herniology and a variety of vein sclerosis techniques. Gedney (1937) applied these injection techniques to joints, the first being the sacroiliac joint. He maintained the term sclerotherapy, which remained in use until the 1950s. In that same year, Schultz (1937) described, in the *Journal of the American Medical Association*, a treatment for subluxation of the temporomandibular joint.

In the mid 1950s, George Hackett published a number of articles based on his more than 20 years' experience, culminating in his book *Ligament and Tendon Relaxation Treated by Prolotherapy* (Hackett 1956), where he claimed an 82% cure rate in a population of 1600 people with back pain (Hackett & Huang 1961). In 1983, Liu confirmed experimentally increases in ligament junction strength and diameter of collagen fibrils.

In 1995, prolotherapy was renamed by some as RIT (regenerative injection therapy), or "the injection of growth factor production stimulants to promote regeneration of normal cells and tissue" (Linetsky & Manchikanti 2005; Reeves et al. 2008).

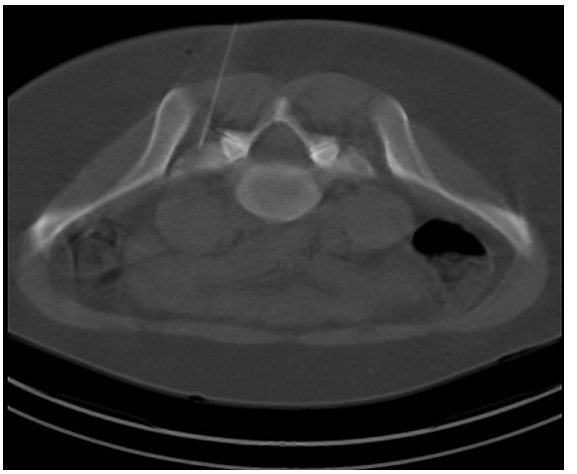

Fig. 7.11.1 • CT scan of prolotherapy in the dorsal interosseous ligament of the sacroiliac joint. Radio-opaque contrast can be added to demonstrate correct placement of the hypertonic dextrose solution and local anesthetic. Courtesy of H. Van der Wall, and L. Wong.

Wound healing, repair and regeneration

An idea of tissue healing and repair is necessary to understand better the effects of prolotherapy.

Wound healing and repair of injured tissues follows three stages (inflammation, matrix deposition, and remodeling) in healthy individuals (Hildebrand et al. 2005). Wound healing generally leads to repair, and in many cases allows return to at least partial function of the injured tissue, but not to tissue regeneration. The repair process leads to a loss of function as a result of scar tissue formation. This is an important factor when dealing with connective tissue that functions in a mechanically active environment. The repair of connective tissue by scar formation – ultimately healing by second intention – may restore connective tissue to its pre-injury length, but will not provide adequate (pre-injury) tensile strength in ligaments and tendons (Reeves 2000; Linetsky & Manchikanti 2005).

The inflammatory phase

Following an acute overt injury there is pain and bleeding. The latter is repaired with the formation of a fibrin clot, which prevents further bleeding and provides a provisional matrix for migrating cells. Blood clotting also releases pro-inflammatory substances, including components of the clotting cascade, cytokines and growth factors released from other cells such as platelets. This contributes to the subsequent migration, localization, and proliferation of other cells (mesenchymal cells, fibroblast-like cells, etc.), which sets the stage for the second phase of the repair process.

The matrix deposition phase

Once the fibrin clot is consolidated and the influx of a subset of cells and deposition of these new cells is established, the deposition of matrix molecules can begin. The purpose of matrix formation is to bridge the damaged area with residual ligamentous tissue. Two points need to be considered:

1. The tissue deposited attempts to bridge the injured area, regardless of the tissue structure it attempts to gap or repair.
2. The changes in the matrix deposited early in the process lead to the organization of deposited matrix that is different from normal tissue. In mechanically active tissues this will result in a severe compromise of the tensile strength of the new tissue formed: scar tissue is not as strong as the original ligamentous tissue.

In addition to matrix deposition in the early stage of healing, there is an increase in cellularity and in vascularity (Bray et al. 1996) due to the release of angiogenic factors in the early postinjury stages. Increased vascularity generates the influx of new micro-vessels. Those connective tissues with endogenous microvasculature will heal well, whereas those that are poorly vascularized (e.g., menisci) do not heal well. In the early stages of scar tissue formation there are almost no neural elements, and therefore minimal regulation of fibroblast-like cells or microvasculature.

The remodeling phase

This is a much slower process, which involves not only alterations in the remodeling of the existing matrix but also gene expression, cellularity, vascularity, and innervation (Hildebrand et al. 2005). The material deposited early is reorganized to suit the mechanical demands of the injured tissue. In the case of ligament, the organization of fibrils becomes oriented towards the axis of the ligament, whereas in other tissues such as skin, a more

basket-weave arrangement takes place, which provides strength in multiple directions. This process may take months or even years, and the composition of the repaired tissue changes with time, as does the gene expression phenotype.

The advent and use of erythrocyte growth factor (erythropoietin) to stimulate red cell proliferation in patients with chronic anemia and even in preparation for acute blood loss in surgery has led to the study of growth factors and their effect in both musculoskeletal medicine and other areas outside medicine, such as endurance sports.

Improved understanding of the role of growth factors in tissue regeneration and healing is compatible with the traditional inflammatory reaction theory and takes it to a new dimension. Prolotherapy now includes the injection of external growth factors – blood, platelet rich plasma (PRP), adult stem cells, or the injection of growth factor stimulators (traditional prolotherapy solutions).

The application of growth factors to stimulate cell proliferation and extracellular matrix synthesis in tendinopathy has been described by Wang and colleagues (2006) and can represent a new look at the mechanism of action of prolotherapy solutions. The transplantation of mesenchymal stem cells into injured tendons has been shown to promote tendon healing in laboratory animal models (Smith & Webbon 2005). The injection of growth factors should produce structural changes in the tissues injected, and these changes result in improved mechanical quality and function. These changes have not been conclusively proven to date, but the possible role of growth factors represents an exciting development pathway. Further systematical study of the topic is required before definite statements can be made.

Mechanism of action and substances injected

Two types of substance are used in prolotherapy. The first is injection of growth factor-containing substances. Examples of this include injection of blood, and injection of mass-produced recombinant growth factors, PRP and mesenchymal stem cells. The second method is stimulation of growth factor production, in which the injected solution initiates production of growth factors (dextrose, inflammatory agents that initiate an inflammatory cascade to produce growth factors), and plasmid DNA (Reeves 2000).

In the classical understanding of the inflammatory reaction theory, there are four types of solutions, grouped according to the suspected mechanism of action (Banks 1991):

1. Osmotic (e.g., hypertonic dextrose) solutions are thought to provoke cell dehydration, with subsequent cell lysis, release of cellular fragments, which in turn attract granulocytes and macrophages. In addition dextrose could cause glycosylation of cellular proteins.
2. Irritants (e.g., phenol) have a phenolic hydroxyl group that is believed to alkylate surface proteins; these either become antigenic or are damaged, and in turn attract granulocytes and macrophages.
3. Chemotactics (e.g., sodium morrhuate) are chemically related to inflammatory mediators such as leukotrienes and prostaglandins, and possibly undergo conversion to these substances to mediate the inflammatory response.
4. Particulate irritants (e.g., pumice flour) are believed to attract macrophages, leading to phagocytosis.

Injections of inflammatory proliferant solutions in connective tissues have demonstrated ligament thickening, hypertrophy of the bone–tendon unit and the strengthening of tendon and ligament in animal studies (Hackett 1956; Liu et al. 1983; Ongley et al. 1988). The injection of hyper- or hypo-osmolar dextrose induces cells to proliferate and produce a number of growth factors. RIT was coined to reflect currently prevailing anatomic and pathophysiological trends in nomenclature. It stimulates chemomodulation of collagen by repetitive induction of inflammatory and proliferative stages leading to tissue regeneration and repair, thus increasing tensile strength, elasticity, mass and load-bearing capacity of collagenous connective tissues. This makes RIT a viable treatment for painful chronic enthesopathies, tendinosis, ligament degeneration, and laxity (Linetsky & Manchikanti 2005).

In retrospect, we can say that the original concept of prolotherapy solutions triggering the inflammatory cascade was overly simplistic. The mechanism of action is now considered to be multifaceted, and includes any or all of the following components (Klein et al. 1989; Reeves 2000; Yelland et al. 2004; Linetsky & Manchikanti 2005):

1. Cellular and extracellular matrix damage induced by mechanical needle injury stimulates the inflammatory cascade, which in turn governs the release of growth factors.

2. Compression of cells by a relatively large volume of external fluid, as well as cell expansion or constriction due to osmotic properties of the solution injected that stimulates the release of intracellular growth factors.
3. Chemomodulation of collagen through inflammatory, proliferative, regenerative/reparative responses induced by the chemical properties of the solutions injected and mediated by cytokines and multiple growth factors.
4. Chemoneuromodulation of peripheral nociceptors provides stabilization of antidromic, orthodromic, sympathetic and axon reflex transmissions.
5. Modulation of local hemodynamics with changes in intraosseous pressure leads to reduction of pain. Empirical observations suggest that a dextrose/lidocaine combination has a much more prolonged action than lidocaine alone.
6. Temporary repetitive stabilization of painful hypermobile joints, induced by inflammatory response to the solutions injected, that provides a better environment for regeneration and repair of the affected ligaments and tendons.
7. Additional possible mechanisms of action include the disruption of adhesions that have been created by the original inflammatory attempts to heal the injury by the large volume of solutions injected. The relatively large volume of chemically nonirritating solution assumes the role of a space occupying lesion in a relatively tight and slowly equilibrating extracellular compartment of the connective tissue.

Indications, contraindications, complications, and risks

The general indication for prolotherapy is chronic musculoskeletal pain: chronic sprains and strains, myofascial syndromes, and arthritis. Whiplash injuries, medial and lateral epicondylitis of the elbow, knee, ankle, shoulder and other joint pain, tendinosis, and musculoskeletal pain related to osteoarthritis all fall within the three general indications. It is based on the premise that pain results from ligaments or entheses, and that these ligaments or entheses can be strengthened by the injection of irritant proliferant solutions into them. More recently, injection of hypertonic dextrose has also been used to restore ligament function rather than to treat of pain (Cusi et al. 2010).

Contraindications include potential local infection, allergies to the local anesthetic used or to some of the substances injected (allergy to shellfish is a contraindication to sodium morrhuate), injection into prosthetic joints, patients on anticoagulants who have a high INR (international normalized ratio).

Complications and risks can be needle related or substance related.

- Needle related:
  - Joint sepsis (Gray & Gottlieb 1983; Pal & Morris 1999). Infection rate post prolotherapy is not greater than post injection of corticosteroids, and is generally accepted at between 1 in 10 000 and 1 in 50 000.
  - Spinal headache (for injections near the spinal canal).
  - Peripheral nerve injury.
  - Pneumothorax (injections around the thoracic wall).
- Substance related:
  - Stiffness or soreness post injection. It typically can last 1–3 days.
  - Allergies (especially to shellfish in sodium morrhuate injections).
  - Chemical arachnoiditis (especially if using phenol in spinal or paraspinal injections).

The adverse effects of prolotherapy injections have been studied by Dagenais et al. (2006). Side effects related to prolotherapy for back and neck pain, such as temporary postinjection pain, stiffness, and bruising were found to be common and benign. Adverse events related to prolotherapy for back and neck pain are similar in nature to other widely used spinal injection procedures, and in general prolotherapy can be considered relatively safe when the more common solutions are used. Further study on this matter is required to replicate Dagenais' findings.

Techniques

There is a wide variety of injection protocols described in the literature. Usually, tender spots are identified with the palpating finger and the skin marked. The number of sites selected for injection, the composition of the proliferant (dextrose-based or dextrose in combination with other substances, often phenol and glycerin), and the volume of

injectate varies, but is generally 0.5–1.00 ml per site injected. Injections are repeated regularly at varying intervals until the desired effect is achieved, with a maximum of weekly injections for up to 6–12 weeks. Injection may or may not be associated with manipulation. A bleb of local anesthetic is used sometimes, but not always (Reeves et al. 2000).

Outcomes and clinical evidence

In a systematic review of prolotherapy for chronic musculoskeletal pain, Rabago et al. (2005) stated in their conclusion that "there are limited high-quality data supporting the use of prolotherapy in the treatment of musculoskeletal pain or sport-related soft tissue injuries". Positive results compared with controls have been reported in randomized and nonrandomized controlled trials. Further investigation with high-quality randomized controlled trials with noninjection control arms in studies specific to sport-related and musculoskeletal conditions is necessary to determine the efficacy of prolotherapy. Literature interpretation is hampered by the variety of solutions and the variety of methods used. Nevertheless, there are several areas of literature in which the unique advantages of prolotherapy are being demonstrated (accessibility and low cost compared to alternative therapies such as surgery), to the point where close observation for follow-up studies is warranted.

A selection of some quality studies published so far follows, regardless of outcome, for specific conditions. There is a much wider body of published research, but its quality is variable and levels of evidence poor.

Lateral epicondylosis. Rabago et al. (2009) have identified strong pilot-evidence supporting the use of dextrose, polidocanol, whole blood, and PRP injections in the treatment of lateral epicondylosis. Prolotherapy in this summary includes under its umbrella all regenerative methods by injection including dextrose-based, inflammation-based, platelet/WBC based (platelet-rich plasma), adult stem cell-based, and essentially any other injection method in which either growth factors are stimulated or disrepair factors are blocked (as was mentioned earlier).

Achilles tendinosis. Sweeting & Yelland (2009) have found that prolotherapy alone is more effective than eccentric loading exercises – at present the "gold standard"– for chronic Achilles tendinosis. The combination of both treatments is again superior to either of them individually. A nonrandomized study of 32 consecutive patients treated with intratendinous 25% dextrose injections (four injections on average) identified improvement of pain for activities of daily living (ADL) of 84%, and for sporting activity (71%). While not a randomized trial, a 94% (30 out of 32) follow-up rate at 12 months (4.5–28) suggests effective treatment (Maxwell et al. 2007).

Groin pain. A study of 24 elite level athletes (22 rugby, 2 soccer) with chronic groin pain, failure of all standard therapies, and failure to play at high level was reported by Topol et al. (2005). Twenty-two out of 24 returned to full play in sustained fashion. This study was then in essence repeated with 48 additional nonelite athletes, with identical results (Topol & Reeves 2008).

Plantar fasciitis (*fasciosis*). A small case series of 20 consecutive patients reports good to excellent results in 16 patients, which compares favorably with extracorporeal shock wave therapy (Ryan et al. 2009). However, further larger studies are necessary before confirming its effectiveness.

Low back pain. Most published clinical studies of prolotherapy are for low back pain. They include nonspecific low back pain, sciatica, and sacroiliac disorder. The five randomized control trials published (Mathews et al. 1987; Ongley et al. 1987; Klein et al. 1993; Dechow et al. 1999; Yelland et al. 2004; Dagenais et al. 2007), are of unequal quality and significance, and may be subject to different interpretations. In a recent study, Yelland and colleagues (2004) found that both injections of normal saline and dextrose solution resulted in a significant improvement, but that there was no statistically significant difference between normal saline (placebo) injections and prolotherapy. This highlights the difficulty of finding an appropriate placebo, because dry needling a ligament can cause an inflammatory reaction. It is therefore not a real placebo but a different intervention. Several consecutive case series since then have confirmed the positive clinical effects of prolotherapy (Hooper & Ding 2004; Wilkinson 2005; Cusi et al. 2008). These results need to be confirmed with well-designed randomized clinical trials that compare prolotherapy to a real placebo injection.

Patellar tendinosis. Two pilot studies (Alfredson & Ohberg 2005; Volpi et al. 2007) suggest that either polidocanol or PRP are effective to reduce pain and improve function. Again, this initial work needs to be completed with larger randomized trials.

Future challenges

While there is a considerable body of literature, the standard of the published research is of unequal quality. Techniques vary widely, as do substance injected, volumes, and frequency. Many studies can only be considered initial, and while promising, they need to be confirmed with soundly designed and conducted randomized trials.

One difficulty for the advocates of prolotherapy is the almost general lack of randomized controlled trials, with conditions (technique, protocol, inclusion and exclusion criteria) that can be replicated. The difficulty of how to arrange real placebo injections is a definite challenge. Comparing injection groups to noninjection groups is hardly randomization, but as mentioned above, a dry needle or an isotonic solution can produce a mechanical injury and generate an inflammatory response.

The clinical expertise already gathered in the practice of prolotherapy needs the back-up of evidence-based research and experts' consensus to gain acceptance in mainstream medical practice, in keeping with the principles of evidence-based medicine (Sackett & Rosenberg 1995), for the benefit of all.

Summary and conclusion

Prolotherapy for treatment of musculoskeletal pain has been used for over 50 years. Present evidence with inclusion of systematic reviews, randomized and nonrandomized evidence indicates effectiveness of RIT in painful enthesopathies. The role of prolotherapy in "mainstream" medicine will improve with further quality research, including standard protocols, properly conducted randomized trials, patient selection, and defined outcome measures.

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