According to the World Health Organization, musculoskeletal injuries are the most common cause of severe long-term pain and chronic physical disability. In the United States, soft tissue trauma accounts for 45% of injuries reported in the orthopedic clinical settings. Among physically active individuals, at least 80% of musculoskeletal injuries are directly related to physical activity, and more than 85% of injuries sustained by athletes are soft tissue injuries. Thus, effective treatment of soft tissue trauma is essential for physically active individuals and competitive athletes.

Prolotherapy (PrT) is a treatment option for a variety of musculoskeletal conditions.

**Background**

George S. Hackett, MD, was an Ohio trauma surgeon considered to be the originator of PrT. He found that injection of a hypertonic sugar solution around ligaments could reduce back pain related to weakened articular ligaments. Hackett believed that the proliferant solution would stimulate the production of fibrous tissue, thereby strengthening the ligaments. He noted that the treatment provided satisfactory results immediately.

PrT is believed to strengthen damaged ligaments or tendons through the stimulation of fibrous tissue synthesis. Treatment with PrT generally includes 3–6 injections of a small volume of proliferant solution around the involved tendon and ligament attachment sites at 4–6 week intervals period. The treatment response will vary according to injury severity, which determines the amount of collagen synthesis that is necessary for tissue repair. Concomitant administration of therapeutic exercise is recommended to enhance the effectiveness of the injection.

Several studies of PrT have reported stimulation of healing for a variety of musculoskeletal conditions, including epicondylitis, Achilles tendonopathy, chronic groin pain, patellar tendonopathy, sacroiliac instability, spinal stenosis, recurrent ankle sprains, and ankle instability. Although most commonly used to treat chronic conditions, PrT may be administered during the acute phase of tissue healing to augment the inflammatory response; however, some experts recommend that the treatment should not be initiated until 24–28 hours postinjury to allow the swelling to subside.

There are other injection treatments that are based on the same healing theories.
as PrT, which include platelet-rich plasma injection, polidocanol injection, and autologous whole blood injection. These therapies appear to provide beneficial effects for sport-related tendinopathies, but more research is needed to confirm their effectiveness and safety.

**How Does Prolotherapy Work?**

PrT injections are believed to promote ligament and tendon hypertrophy, which increases capacity to withstand imposed stresses. Dextrose (a form of glucose) and P2G (phenolglycerine-glucose) are two common PrT solutions. Dextrose solution is believed to produce osmotic rupture of cells in the vicinity of the injection, and P2G is believed to produce cell irritation, but the precise mechanisms of action have not been determined. Lidocaine is often included in the proliferant solution to reduce pain associated with the injection procedure (see Figure 1).

A plausible theory for the mechanism of PrT action is stimulation of interactions among fibroblasts, granulocytes, macrophages, and growth factors. In response to the treatment, the ligament or tendon fibro-osseous junction may be strengthened. The healing process typically requires approximately six weeks, with most of the tendon or ligament strengthening occurring during the 2–4 week period following PrT injection.

The reported side-effects of PrT are minimal, but spinal headaches are possible, and pneumothorax is a risk associated with thoracic injection. Skin, blood, or joint infection is a possible complication for any injection. Other risks include increased pain, stiffness, bleeding, bruising, swelling, and nerve, tendon, or ligament injury. There are no absolute contraindications for PrT injection, but active infection (e.g., shingles) and bleeding disorders present potentially greater risk for an adverse consequence.

**Recovery From Treatment**

The response to PrT injections involves three phases. Phase I spans from the time of injection through the fourth postinjection day. During this “acute inflammation” phase, a patient can engage in physical activity (e.g., walking). Phase II is defined as the fifth through the tenth postinjection day. During this “scaffolding” phase, the patient is advised to avoid all physical activity. Because the tissue is weakest during this phase, stretching and heavy weightlifting should be avoided to prevent tissue disruption. Phase III begins on the tenth postinjection day and terminates at the next PrT treatment. During this “repair” phase, an athlete can participate in sport-specific activities. The next injection would be administered after 4–6 weeks of tissue healing time.

**Research Evidence**

Low back pain and sacroiliac joint dysfunction are common indications for administration of PrT. As far back as 1957, P2G solution has been advocated as an effective method for reduction of pain associated with sacroiliac dysfunction and neck strain. Shortly thereafter, PrT with P2G was reported to reduce pain associated with low back pain, whiplash, and nontraumatic headache. Recent evaluation of PrT effectiveness has involved dextrose injection. In 1988, Bourdeau injected 24 low back pain patients with 12.5% dextrose at 3–10 treatment sessions. Nineteen of the 24 patients reported excellent to good pain relief over a posttreatment evaluation period of 2–5 years. Ongley et al. studied four patients with knee pain and knee ligament laxity. They injected the patients with 30–40 cc of P2G. A peppering technique (i.e., movement of the needle in a clockwise manner to cover a more extensive area) was used to inject the anterior cruciate ligament, posterior cruciate ligament, medial collateral ligament, and lateral collateral ligament attachment sites. The treatment responses were interpreted as positive on the basis of decreased knee laxity, decreased knee pain, and improvement in subjective knee function. All four patients demonstrated improved range of motion, and more than 90% experienced improvement in knee function.

In 1982, Naeim et al. reported that the combination of lidocaine and dextrose was more successful than lidocaine alone for treatment of sacroiliac dysfunction (86% success as compared to 44%). In 2008,
Cuzi et al.\textsuperscript{16} reported that 25 subjects with sacroiliac dysfunction demonstrated significant improvement 3, 12, and 24 months following a series of three dextrose injections. Similar findings were reported from a double-blind, randomized study of patients with lateral epicondylitis.\textsuperscript{13} After having received injections of dextrose and sodium morrhuate, patients reported less pain and greater strength compared to control patients. Topol et al.\textsuperscript{7} reported that dextrose injection reduced chronic groin pain among elite rugby and soccer athletes.

In 2010, a systematic review of prolotherapy treatment for chronic low back pain located only 5 randomized clinical trials that met inclusion criteria.\textsuperscript{17} Dagenais et al.\textsuperscript{17} concluded that PrT injection alone was not sufficient to reduce low back pain. Another systematic review of research on PrT, platelet rich plasma, and two other types of injections for treatment of lateral epicondylitis concluded that PrT was effective and that it was the easiest treatment of the four for patients to receive.\textsuperscript{8} The only disadvantage of PrT reported in this review was a longer healing response compared to the other types of injection.

**Discussion**

The available literature suggests that PrT may be an effective treatment for ligament and tendon injuries, but there is a lack of randomized clinical trials that have compared PrT to a placebo or alternative treatments that do not involve injection.\textsuperscript{17} The literature contains numerous reports of positive outcomes from administration of PrT to patients with chronic, debilitating pain.\textsuperscript{4,7,9,12,15,16}

Physician experience may play an important role in the outcome realized from PrT. A one-year PrT training course is available, but most physicians learn about PrT through continuing education or from observing patient responses to PrT administered by other physicians. A physician who has a high level of expertise in PrT may be hard to locate and may not be readily accessible.\textsuperscript{9}

More research is needed to understand the mechanism of PrT action compared to that of saline injection (or other control solution injection). Future studies should also consider the experience of the physician who administers PrT.

Unlike platelet-rich plasma injection, PrT is not prohibited by the World Anti-Doping Agency. Furthermore, PrT does not present the problem of connective tissue weakening associated with corticosteroid injection. Thus, athletic trainers and therapists should not be reluctant to have an athlete referred to a physician who administers PrT to promote tendon and ligament healing.

**References**


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