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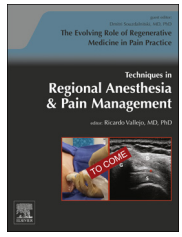

Everything old is new again: New developments in prolotherapy

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ABSTRACT

Prolotherapy, or fibroproliferative therapy, is a regenerative injection therapy, first popularized in the 1940s and 1950s. Unfortunately, the combination of "better" surgical techniques and a series of high-profile medical catastrophes by poorly trained providers relegated the technique into the "fringe" arena. However, recent recognition of the failure of surgical interventions, combined with better technology and a burgeoning interest in the continuum of regenerative injection options, has renewed the interest and research into this "old" technique.

Prolotherapy, also known as *Regenerative Injection Therapy* (RIT) or *Sclerotherapy*, is an interventional pain management technique that repetitively provides a mild neurolytic effect followed by a complex restorative process with biochemically induced collagen regeneration.

History

Prolotherapy has a long history of use to treat painful conditions. Cornelius Celsus (25 BC to 50 AD) described the injection of irritating substances, specifically saltpeter (potassium nitrate), as a cure for hydrocele.[1] In 1836, Joseph Pancoast, from Jefferson Medical College, was the first American surgeon of prominence to treat hernias by injecting the sac with irritation solutions, to create an inflammatory response.[2] Earl Gedney, in 1937, was the first to describe the injection of irritants to treat ligament pathology in unstable painful knee and sacroiliac joints (SIJs).[3] Furthermore, in the late 1930s, J. H. Kellgren systematically studied pain from deep somatic structures by injecting hypertonic saline into volunteer healthy medical students; he published maps of referred pain from muscles, deep fasciae, tendon sheaths, periosteum, and ligaments, implicating them as a source of both local and referred pain. George Hackett, in 1955, published the first experimental research on animal ligaments injected with irritating solutions, demonstrating the ability to induce hypertrophy and hyperplasia within connective tissue.[4] In 1956, Hackett concluded that "sclerotherapy" implied "scar formation," and instead, he introduced the term, "fibroproliferative therapy" or "prolotherapy" as "the rehabilitation of an incompetent structure by generation of new cellular tissue."[5]

Pathophysiology

Ligaments and tendons have a crimped, wavelike appearance under a light microscope, which unfolds during initial collagen loading. After elongation beyond 4% of the original length, ligaments and tendons lose elasticity and recoiling capability, becoming permanently lax, which leads to joint hypermobility with instability. The ligament and tendon response to a trauma is both inflammatory and regenerative

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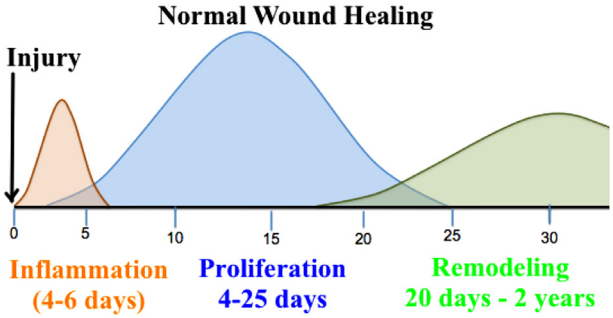

Fig. 1 – The sequence of events in wound healing. (*Image courtesy*: Andrea Trescot, MD). (Color version of figure is available online.)

in nature (Figure 1). There are following 3 phases to the healing response:

(1) *Hemorrhage with inflammation*—there is an increase in neovascularization and neoneurogenesis.
(2) *Matrix and cellular proliferation*—hypertrophic fibroblasts create a dense, disorganized collagenous connective tissue matrix.
(3) *Remodeling and maturation*—there is an alignment of the fibers along the long axis of the structure, cross-linking of the fibers, and absorption of the neovascularization.

This process is inhibited by anti-inflammatory medications —steroid and nonsteroidal anti-inflammatory drugs. The resulting persistent inflammation at the *entheses* (the bone/tendon/ligament attachments) is termed an *enthesopathy*.

When hypertonic dextrose is injected into the richly innervated connective tissue of a ligament or tendon, there is an inflammatory response, stimulating the production of fibroblasts as well as a hyperosmolar neurolytic action of the 12.5%, 20%, and 25% dextrose on small myelinated and unmyelinated C fibers.[6-8] The neovascularization of this enthesopathy is likely also painful, and prolotherapy has been proposed to sclerose these vessels as well.

Regenerative injection therapy

With the recognition of the role of enthesopathies as an underlying cause of chronic pain, there have been a variety of injection therapies that have expanded the concepts of prolotherapy. This continuum of treatments has been grouped under the heading of *Regenerative Injection Therapy*, defined as "innovative medical therapies that will enable the body to repair, replace, restore, and regenerate damaged or diseased cells, tissues, and organs." For example, *prolozone* uses the injection of ozone gas (1%-3%) to stimulate healing and eliminate pain in injured soft tissues and joints.[9] Placental-derived *stem cell factors* and amniotic tissue can be injected into the ligament attachments. Autologous blood can be collected, spun down, and the subsequent *platelet-rich-plasma* injected; techniques for collecting autologous *stem cells* from the *bone marrow* and *adipose tissue* have also been developed.[10]

Indications

Prolotherapy is indicated for almost any ligament laxity or enthesopathy. Just a few examples include treatment of the enthesopathy that causes rotator cuff tendinopathy,[11,12] lateral epicondylitis,[13] whiplash,[6,14] temporomandibular joint (TMJ) dysfunction,[15,16] knee osteoarthritis and ligament instability,[17,18] meniscal tears,[19] Osgood-Schlatter disease,[20] plantar fasciitis,[21] Achilles tendonitis,[22] sacroiliac and pelvic girdle dysfunction,[23,24] axial low back pain after spinal surgery,[25] and chronic low back pain.[26]

The Table shows some of the indications that have been described for prolotherapy.

Evidence

Until recently, prolotherapy has been considered a "fringe" technique. Because of its early beginnings, prolotherapy was not initially subjected to the rigors of formal education and "evidence-based medicine," and it was widely practiced by providers with little spine injection training. Not surprisingly, in the late 1950s, there were several cases of postinjection arachnoiditis, 2 of which were fatal,[27] and the technique was subsequently condemned. However, a small group of practitioners kept the concept alive, and the technique began a slow resurgence in the late 1980s.

Several early, randomized controlled trials (RCT) of prolotherapy were performed, but the results have been inappropriately interpreted. The first RCT, in 1987, evaluated prolotherapy pain in conjunction with manipulation.[28] A total of 35 patients of 40 in the treatment group (0.2-0.4 mL of dextrose/phenol/glycerin (DPG) solution injected in a fan at each enthesis contact site followed by manipulation) and 16 of 41 in the control group (normal saline injections and sham manipulation) achieved >50% improvement in pain and disability, sustained at 6 months. The second RCT, in 1993, compared lidocaine/DPG solution with lidocaine/normal saline control and manipulations.[29] Using 30 mL of either solution for each treatment session, 0.5 mL was deposited

Table – Selected indications for prolotherapy.

Osteoarthritis (small and large joints)
Ligament instability
Tennis elbow
Temporomandibular joint dysfunction
Rotator cuff disease
Upper and lower back pain
Whiplash injury
Failed back syndrome
Osgood-Schlatter disease
Sacroiliac joint pain or dysfunction
Pelvic girdle dysfunction
Coccydynia
Meniscal tears
Posttraumatic groin pain
Anterior cruciate ligament
Achilles tendinopathy
Plantar fasciitis