10.5005/jp-journals-10046-0064

REVIEW ARTICLE

Prolotherapy: From Glorious Past to Promising Future

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ABSTRACT

Prolotherapy, a nonsurgical regenerative injection therapy, is becoming increasingly popular among the pain physicians as well as patients. The current theory suggests that the prolotherapy mimics the natural healing process of the body by initiating a local inflammatory cascade, which triggers the release of growth factors and collagen deposition. Although the clinical literature on prolotherapy had been published since last 80 years, the quality, number, and research have increased since the 1990s. The growing body of evidences suggests its use in osteoarthritis, low back pain, and tendinopathies. With recent advances in stem cell therapy and regenerative medicine, prolotherapy will play a greater role in the treatment of chronic degenerative conditions and sports injuries.

Keywords: Chronic pain, Osteoarthritis, Prolotherapy, Regenerative injection therapy, Stem-cell therapy, Tendinopathy.

How to cite this article: Mathankar NK, Chansoria M. Prolotherapy: From Glorious Past to Promising Future. J Recent Adv Pain 2017;3(1):41-45.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

Prolotherapy is a nonsurgical regenerative injection therapy (RIT) for chronic musculoskeletal pain. It introduces small amounts of an irritant solution to the site of painful and degenerated joints, ligaments, tendon insertions, and in adjacent joint spaces in order to promote growth of normal cells and tissues. Irritant solutions commonly used for injections are dextrose, combinations of polidocanol, manganese, zinc, human growth hormone, morrhuate sodium, pumice, ozone, glycerin, phenol, or platelet-rich plasma (PRP). There are many types of prolotherapies including Hackett–Hemwall, subcutaneous, PRP, prolozone, and stem cell prolotherapy using either bone marrow or adipose tissue.

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George S Hackett[1] had coined the term prolotherapy and described it as follows: "The treatment consists of the injection of a solution within the relaxed ligament and tendon which will stimulate the production of new fibrous tissue and bone cells that will strengthen the 'weld' of fibrous tissue and bone to stabilize the articulation and permanently eliminate the disability." The name of this therapy has changed over time with evolved hypotheses and understanding of possible mechanisms of action. The term "sclerotherapy" has been used because early solutions were thought to be scar forming. It is also called RIT. However, based on the presumed "proliferative" effects on chronically injured tissue, "prolotherapy" is currently the most commonly used term.

MECHANISM OF ACTION

Although the exact mechanism of action is not understood, the current theory suggests that the prolotherapy mimics the natural healing process of the body by initiating a local inflammatory cascade, which triggers the release of growth factors and collagen deposition. Prolotherapy promotes the three stages of healing and restoration: Inflammation, proliferation, and tissue remodeling (Fig. 1).

This is accomplished when induced cytokines mediate hemomodulation, which leads to proliferation and strengthening of new connective tissue, joint stability, and a reduction in pain and dysfunction. Supported by pilot-level evidence, the three most commonly used prolotherapy solutions have been hypothesized to act via different pathways: Hypertonic dextrose by osmotic rupture of local cells, phenol–glycerine–glucose (P2G) by local cellular irritation, and morrhuate sodium by chemotactic attraction of inflammatory mediators and sclerosing of pathologic neovascularity associated with tendinopathy. The potential of prolotherapy to stimulate release of growth factors favoring soft tissue healing has also been suggested as a possible mechanism.

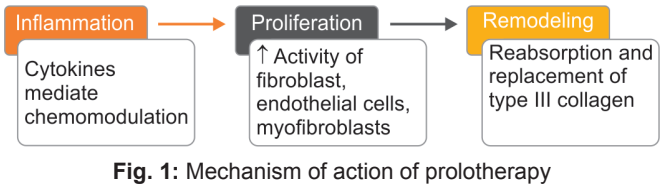

Fig. 1: Mechanism of action of prolotherapy

GLORIOUS PAST

Hippocrates himself practiced the theory of prolotherapy in the 5th century BC by treating unstable joints by cauterizing the ligaments with a hot metal rod. As one of the first experiments utilizing the body's own healing mechanism to heal connective tissues, Hippocrates proposed the hypothesis that induced inflammation of injured ligaments will lead to self-repair.[2] In the 1st century BC, Celsus, a Roman encyclopedist, described the treatment of hydrocele around the testicle via the injections of a potassium nitrate solution. Centuries later in 1832, Dr George Heaton realized that he could tighten the connective tissues around the inguinal ring by injecting them with *Quercus alba* (white oak) solution in patients of inguinal hernia. These injections of hernias, varicose veins, and hemorrhoids were eventually known as sclerotherapy. In 1936, Earl Gedney, an osteopathic surgeon, expanded the technique of sclerotherapy by injecting medial and lateral collateral ligaments of unstable knees with a solution known as neoplasmoid. In 1937, Louis Schultz, found that the sylnasol (sodium psylliate), a 5% solution of fatty acid could induce fibrogenesis of the injured tissues without causing adverse effects on noninvolved tissues. He started using this solution and stabilize temporomandibular joints.

In 1939, George S Hackett applied the concept of tendon pathology and ligament laxity to chronic musculoskeletal pain, coined the term prolotherapy, and published a medical book entitled "Ligament and Tendon Relaxation Treated by Prolotherapy." Over the next 3 decades, he published various research papers documenting the success rate of prolotherapy in the elimination of chronic musculoskeletal pain including results on 1,800 patients with chronic low back, and noted an 82% cure rate 12 years after treatment of prolotherapy. In 1955, Gustav A Hemwall met Dr Hackett at an American Medical Association meeting. Later, Dr Hemwall and Hackett promoted prolotherapy at various medical meetings. Their technique is known as the Hackett–Hemwall technique of prolotherapy. Dr Hemwall was the main proponent of prolotherapy for the next 30 years, until his death in 1998.[3]

The first randomized controlled trial (RCT) was published in 1987; however, until then clinicians have reported the results of more modest, pilot-level clinical trials. A 2005 systematic review of prolotherapy for all indications found 42 published reports of clinical prolotherapy trials since 1937. A total of 36 of the studies were case reports and case series that included 3,928 patients. Studies using the present-day solutions started to appear with P2G in the 1960s, dextrose in the 1980s, and morrhuate sodium in the early 1990s.[4] These studies were lacking control groups, randomization, and fixed protocols. However, overall, these studies assessed the effectiveness of prolotherapy in "real-life settings" where prolotherapists select the patients and decide the injection protocol for the individual patient. In these early studies, the efficacy of prolotherapy was assessed for indications of low back pain (LBP) (72%), knee osteoarthritis (OA), shoulder dislocation, neck strain, costochondritis, lateral epicondylosis, and fibromyalgia.

PRESENT

Interest in prolotherapy has intensified over the past two decades among both physicians and patients. As a result, the number and quality of research activities in prolotherapy improved in the 1990s for the treatment of OA, LBP, and tendinopathy including lateral epicondylosis, Achilles, adductor, and plantar fasciitis. Each one of these conditions is a significant cause of pain and disability and is often refractory to best standard-of-care therapies.

OSTEOARTHRITIS

Prolotherapy has been assessed as a treatment for knee and finger OA. A three-arm randomized controlled double-blinded study conducted by Rabago et al[5] found significantly greater improvement in pain reduction, swelling, buckling episodes, and flexion range with dextrose compared with lidocaine injections or exercise. In a recently published analysis, Rabago et al[5] reported that most participants have continued to experience progressive improvement of knee pain, function, and stiffness scores at 2.5 years after the initiation of the study.

A recently published meta-analysis concluded that prolotherapy conferred a positive and significant beneficial effect in the treatment of knee OA. Prolotherapy was found to be superior to exercise alone by a standardized mean difference of 0.81 (95% confidence interval [CI]: 0.18 to 1.45, p = 0.012), 0.78 (95% CI: 0.25 to 1.30, p = 0.001), and 0.62 (95% CI: 0.04 to 1.20, p = 0.035) on the Western Ontario and McMaster Universities Arthritis Index (WOMAC) composite scale; and WOMAC function and pain subscale scores respectively.[6]

LOW BACK PAIN

Four RCTs evaluated prolotherapy for musculoskeletal LBP using a protocol involving injections to the ligamentous insertions of the L4–S1 spinous processes, sacrum, and ileum. Three of these used P2G as the injectant and the fourth used dextrose. Two out of four RCTs reported positive findings compared with control injections. Ongley et al[7] revealed that significantly more subjects in the prolotherapy (88%) group reported at least 50%

reduction in pain severity compared with controls (39%). Prolotherapy group also reported significantly decreased pain and disability levels compared with controls. Klein et al[8] also reported that significantly more prolotherapy subjects (77%) improved by ≥50% on pain or disability scores than controls (53%). Dechow et al[9] and Yelland et al[10] reported no statistically significant difference in improvement in pain among the prolotherapy and control groups. Although overall results are positive, interpretation of these RCTs is difficult because both experimental and control groups received different treatment protocols.

Cusi et al[11] assessed subjects with sacroiliac joint dysfunction and pain, refractory to 6 months or more of physical therapy, and with documented failure of load transfer (disability) at the sacroiliac joint. Injections of dextrose (18%) were delivered in three sets over 12 weeks. Pain and disability scores on three multidimensional outcome measures significantly improved at 26-month follow-up compared with baseline. Khan et al[12] reported significant decrease in average pain score (8.5 to 2.5 points) at 2 months in 37 subjects with refractory coccygodynia with 25% dextrose in up to 3 prolotherapy injection sessions. In a novel study, Miller et al[13] assessed prolotherapy for leg pain due to moderate-to-severe degenerative disk disease in subjects (n = 76) who failed physical therapy and had substantial, but temporary pain relief with two epidural steroid injections. After an average of 3.5 sessions of biweekly injections to the relevant disk space with 25% dextrose with bupivacaine, 43% of responders showed a significant, sustained treatment response of 71% improvement in pain score. Although the studies are not controlled, they show promising results with prolotherapy.

TENDINOPATHY

The most robust data supporting the efficacy of prolotherapy for musculoskeletal conditions, compared with control injections, are for chronic, painful overuse tendon conditions. Independent of location, tendinopathies from repetitive motion and overuse injury share markedly similar histological, sonographic, and clinical characteristics, representing an underlying noninflammatory painful degenerative pathophysiology.

In one double-blinded study, young athletes aged 9 to 17 years with Osgood–Schlatter disease were randomized to dextrose injection, control injection, or to a noninjection group. At 1 year, 84% of the dextrose-treated knees were pain-free compared with 46% of the lidocaine-treated knees.[14] Ryan et al[15] enrolled 99 patients with chronic Achilles tendon symptoms due to degeneration, who had failed all previous therapies. Ultrasound guidance injection into areas of degeneration (hypoechogenicity or tear) with 0.5 mL or less 25% dextrose in one to three spots at each treatment resulted in improvement in pain with everyday living; improvement from 57% at a mean of 28 weeks into treatment to 81% at a mean of 14 months posttreatment was observed.

In a small double-blind RCT with adults with lateral epicondylosis conducted by Scarpone et al,[16] the treatment group was injected at 0, 1, and 3 months with 0.72% sodium morrhuate, 10.7% dextrose, 0.29% lidocaine, and 0.04% sensorcaine. The treatment group showed significant improvement in pain levels compared with patients given saline injection with the same number of needle punctures and volume (91 *vs* 33%). Moreover, extension strength and grip strength were markedly improved in the treatment group. Park et al[17] also reported that injection dextrose (15%) significantly reduces pain.

Ryan et al[18] treated 20 adults of chronic plantar fasciitis refractory to conservative care with an average of 21-month duration of heel pain by ultrasound-guided 25% dextrose injections for an average of three treatment sessions delivered at 6-week intervals. At 11.8 months, pain severity significantly improved at rest, during activities of daily living, and sport activities by 26.5, 49.7, and 56.5 points respectively, compared with baseline on 100-point visual analog scale (VAS), and 16 of 20 subjects reported good or excellent treatment effects.

Topol and Reeves[19] conducted two uncontrolled trials in athletes with chronic groin pain from osteitis pubis and/or adductor tendinopathy. The treatment consisted of monthly injections of 12.5% dextrose with 0.5% lidocaine in abdominal and adductor attachments on the pubis. Substantial reductions in VAS pain and the Nirschl Pain Phase Scale, in 88.8% and 83.3% of patients respectively, were observed at follow-up.

An RCT conducted by Bertrand et al[20] revealed that injections of hypertonic dextrose on painful entheses resulted in superior long-term pain improvement and patient satisfaction compared with blinded saline injection over painful entheses, in treatment of moderate-to-severe rotator cuff tendinopathy due to injury. A retrospective case–control study demonstrated dextrose prolotherapy improved in pain, disability, isometric strength, and shoulder active range of motion in patients with refractory chronic nontraumatic rotator cuff disease.[21]

PROMISING FUTURE

Developments of quantitative ultrasound measures to objectively evaluate soft tissue organization are enabling prolotherapists to better understand the pain sources and enhancing the ability to guide soft tissue interventions.

Ability to inject the substance with finer needles is also leading to improved patient comfort and preference.

High-density PRP (HD-PRP) has shown the ability to enhance musculoskeletal healing and stimulate local microenvironmental regenerative capabilities, by releasing large quantities of platelet-derived growth factor, transforming growth factor-beta 1, and many other growth factors that, when activated, significantly enhance stem/stromal cell proliferation and angiogenesis.[22] Wang-Saegusa et al[23] treated 312 OA patients with a total of three intraarticular injections of PRP. Statistically significant differences were observed at 6 months in the following assessment instruments: VAS, SF-36, the WOMAC, and Lequesne Index. Autologous adipose-derived stem/stromal cells combined with HD-PRP concentrates are found to be very effective in the preclinical use by physicians in the United States. Bone marrow mesenchymal stem cells (BMSCs) also have potential greater than PRP to regenerate cartilage defects in OA, and potentially slow down or improve the disease process. Human studies have documented enhanced treatment outcomes for nonunion fractures, avascular necrosis, and spinal fusions with the utilization of BMSCs.

Closed isolation of the large numbers of stem and stromal cells from the adipose tissues is now possible. These isolated cells permit creation of cell-enriched biocellular grafts with higher numbers of the heterogeneous undifferentiated cells. These grafts can provide an even more potent guided injectable therapy. Overall, regenerative therapy is a novel strategy that has the potential to restore normal structure and function of damaged tissues. At present, clinical studies in regenerative therapy are limited, but clinical trials are now gradually being released, many requiring several years to acquire data, compile, and report.

CONCLUSION

Prolotherapy is becoming increasingly popular globally and is actively used in clinical practice by family or sports medicine physicians, orthopedic surgeons, neurologists, or anesthesiologists. The practice of prolotherapy is supported by positive outcomes in numerous clinical studies. The current understanding of human physiology also validates the proposed mechanism of action of prolotherapy. Recent advances in stem cell research will further increase the use of prolotherapy in treatment and rehabilitation in chronic pain due to degenerative musculoskeletal disorders and sports injury. Although current pharmacologic and regenerative therapies show great promises, limitations still exist. Potential therapies may be developed by exploring more therapeutic targets and methods.

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