How Effective Are Proloterapy In Treating Musculosceletal Pain

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Musculoskeletal diseases occur more frequently as people age. Aging of the U.S. population, higher rates of diagnoses and treatment, increasing medical cost and the cost of higher earnings loss all contribute to the rising burden of musculoskeletal diseases.[1]

Prolotherapy is a practical and efficacious therapeutic strategy to treat ligamentous laxity and related musculoskeletal and arthritic conditions. Prolotherapy has been used in clinical practice for more than 80 years to treat various chronic musculoskeletal conditions. Formalized by Dr. George Hackett in the 1950s.[4-5] Interest in prolotherapy has intensified over the past two decades among both physicians and patients,[6-7] accompanied by an increasing number of published treatment outcome studies that confirm anecdotal findings that prolotherapy is effective in treating many conditions with few adverse effects, including osteoarthritis (OA),[8] musculoskeletal pain,[9] joint pain and laxity,[9] chronic low back pain,[10] refractory lateral epicondylosis,[11] painful overuse tendinopathy, refractory,[9] disabling low back pain,[9] and refractory tendinopathies, and OA.

Prolotherapy is a nonsurgical regenerative injection technique that introduces small amounts of an irritant solution to the site of painful and degenerated tendon insertions (entheses), joints, ligaments, and in adjacent joint spaces during several treatment sessions to promote growth of normal cells and tissues.[13-15] Irritant solutions most often contain dextrose (d-glucose), a natural form of glucose normally found in the body, but may also contain Ácombinations of polidocanol, manganese, zinc, human growth hormone, pumice, ozone, glycerin, or phenol.[5] In severe cases, autologous cellular solutions may also be needed, such as platelet-rich plasma (PRP), bone marrow, or adipose tissue.[16] A major goal of prolotherapy in chronic musculoskeletal conditions is the stimulation of regenerative processes in the joint that will facilitate the restoration of joint stability by augmenting the tensile strength of joint stabilizing structures, such as ligaments, tendons, joint capsules, menisci, and labral tissue. The most common prolotherapy agent used in clinical practice is dextrose, with

concentrations ranging from 12.5% to 25%.20 Dextrose is considered to be an ideal proliferant because it is water soluble, a normal constituent of blood chemistry, and can be injected safely into multiple areas and in large quantity. Hypertonic dextrose solutions act by dehydrating cells at the injection site, leading to local tissue trauma, which in turn attracts granulocytes and macrophages and promotes healing. Dextrose proliferant has been approved for injection by United States Food and Drug Administration but not for prolotherapy; thus, it is currently used in prolotherapy as an off-label substance. The mechanism of action behind prolotherapy is not completely understood. However, current theory holds that the injected proliferant mimics the natural healing process of the body by initiating a local inflammatory cascade, which triggers the release of growth factors and collagen deposition. This is accomplished when induced cytokines mediate chemomodulation, which leads to proliferation and strengthening of new connective tissue, joint stability, and a reduction in pain and dysfunction.[2]

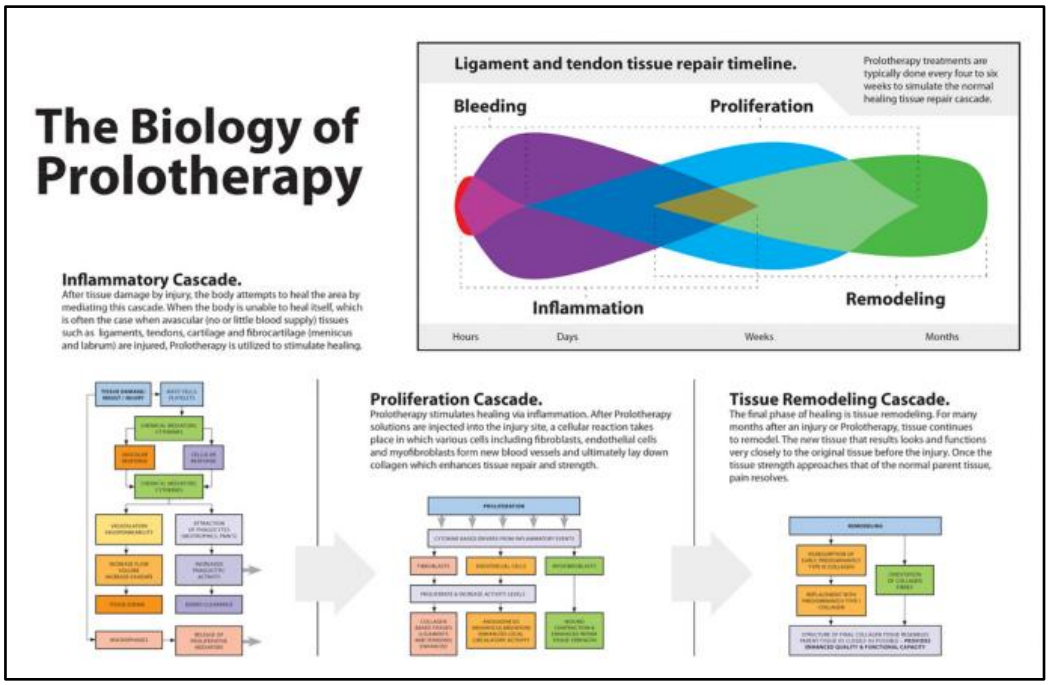

Figure 1.The biology of prolotherapy. Prolotherapy induces the three stages of healing and restoration: inflammation, proliferation, and tissue remodeling.[2]

Figure 1 is a schematic depiction of the application of the therapeutic principle of prolotherapy – encompassing the inflammatory, proliferation, and tissue remodeling phases of the healing and restoration processes of injured ligaments/tendons.[2]

Stimulation of the production of these key growth factors for ligaments, tendons, and cartilage through dextrose prolotherapy could be an inexpensive method of growth stimulation that may prove to be cost effective for the long term.[17] When injected into tissue, exogenous dextrose has been found in animal and human studies to stimulate inflammatory response,[18] ligament size,[19] tendon hypertrophy,[20-22] extracellular matrix,[21-23] fibroblastic proliferation,[21-24] and repair of articular cartilage defects.[24-25] When used clinically, dextrose concentrations higher than 10% operate in part through inflammatory mechanisms, while concentrations less than 10% are considered noninflammatory.[2]

Lane M *et al* reported on the effectiveness of prolotherapy for treatment of lower-limb tendinopathies and fasciopathies and found that there is limited evidence to support prolotherapy for the treatment of these pathologies. Of the studies that were reviewed, only a small proportion were randomised controlled trials, with the majority of studies employing a prospective case-series design using a relatively small sample size and no control or usual care group.[3]

Tendinopathies. The most robust data supporting the efficacy of prolotherapy for musculoskeletal conditions, compared to control injections, are for chronic, painful overuse tendon conditions.[8-9] Independent of location, tendinopathies from repetitive motion, and overuse injury share markedly similar characteristics.[2] Cases of tendinopathies in the Achilles tendon,[2] common elbow extensor, and patellar tendon[2] possess similar histological, sonographic, and clinical features believed to represent an underlying noninflammatory painful degenerative pathophysiology.[2] Histopathology of tendon biopsies in patients undergoing surgery for painful tendinopathy has revealed collagen separation, thin, frayed, and fragile tendon fibrils with lengthwise separation from other fibrils, disruption in cross section, and increase in tenocytes with myofibroblastic differentiation (tendon repair cells), proteoglycan ground substance, and neovascularization.[2] The efficacy of dextrose injections in tendinopathy is believed to involve the initiation of a healing response secondary to cell membrane perturbation that follows a significant change in osmotic pressure between the extracellular matrix and tendon fibroblasts.[2]

OA and degenerative conditions. OA is characterized by progressive breakdown of articular cartilage, proteoglycan degradation, and disruption of the collagen network resulting in joint destruction and loss of function. In addition to genetic and biochemical factors, several external factors have been associated with OA. These include sudden impact, direct trauma,

overuse or repetitive motion injuries, avascular necrosis, corticosteroids, obesity, and ligamentous injury culminating in joint hypermobility and instability. Ligament damage resulting in weakness is an important factor in the development of OA as it prevents normal distribution of weight and increases stress on the articular surfaces of the joint causing cartilage injury and joint degeneration. Ligament laxity and joint capsule disruption increases joint hypermobility and also risk of articular cartilage injury due to loss in the stabilization of joint motion by the ligament structure. Experimental studies have shown the positive effect of hypertonic dextrose in promoting direct intracellular expression of growth factors in tenocytes and fibroblasts.[17] Dextrose prolotherapy may also benefit those with knee OA through the stabilization of interarticular ligaments by its positive effect on joint mechanics to promote articular cartilage recovery and improvement in range of motion.[17]

Spinal and pelvic pain. In approximately 90% of patients, low back pain is mechanical in nature, typically originating from overuse, straining, lifting, or bending that results in ligament sprains, muscle pulls, or disk herniation.99 The popular understanding of back pain is disk herniation as a frequent cause, but to a much greater extent, ligament injury forms the underlying basis.99,100 Ligaments hold the disk in place, and with ligament weakness, the disk is more likely to herniate.

Discogenic leg pain. Dextrose prolotherapy has been effective in treating patients with coccygodynia pain in both case series studies and RCTs. There is Level 1 evidence that dextrose prolotherapy results in significantly greater long-term pain reduction than corticosteroid injection in patients with SI joint pain,[26] and Level 2 evidence of comparable short-term pain reduction versus corticosteroid injection in patients with SI pain.[27] There is strong Level 4 evidence of significant and comparable improvement in pain and disability between patients with chronic cervical, thoracic, or lumbar pain actively involved versus not involved in litigation.[28] There is Level 4 evidence of significant pain reduction and association between changes in pain level and radiographical findings in patients with post-motor vehicle accident neck pain and disability,29 significant reduction in pain and disability in patients with low back and pelvic pain,[30] and significant pain reduction in patients with coccygodynia.

Myofascial pain syndrome. The theoretical basis for dextrose prolotherapy in myofascial pain syndrome (MPS) suggests that since MPS is a state of deficient energy metabolism, dextrose injection into myofascial trigger points may stimulate energy production to relieve

the associated pain syndrome.93 Reviewed Studies. In an RCT, patients received injections of dextrose 5%, saline solution, or lidocaine 0.5%. At 7 days postinjection, dextrose-treated patients were improved from baseline in pain (VAS) and pressure threshold tolerance (algometer; kg/cm2) (P , 0.05); saline and lidocaine patients did not show improvement from baseline on either measure.[2]

The high quality evidence to support the use of dextrose Prolotherapy for musculoskeletal pain. (See Table 1.) There is level 1 and grade A evidence to support the use of dextrose Prolotherapy in the treatment of Osgood-Schlatter disease, myofascial pain syndrome, knee osteoarthritis, tendinopathy and pain involving the sacroiliac joint. Level 3 and grade B evidence exist to support the use of dextrose Prolotherapy for chronic and/ or diffuse musculoskeletal pain involving the spine and peripheral joints. Of the nine randomized double-blind controlled clinical trials, seven found dextrose Prolotherapy significantly more effective than saline injections and standard therapies for musculoskeletal pain. The two other double-blind controlled clinical trials showed statistically significant reduction of pain in the pre- and post-dextrose Prolotherapy patients. The 44 case series, comprised of 2,296 areas treated, consistently showed a statistically significant decline in pain levels when before and after dextrose Prolotherapy pain levels were compared using statistical analyses including a matched paired t-test. While these case studies are not comparing dextrose Prolotherapy to another manner of treatment, they have the advantage of assessing the effectiveness of dextrose Prolotherapy that patients and doctors encounter in clinical practice. Though they lack the methodological strengths of randomization and control, the case studies documented in this review show overwhelming positive outcomes for clearly longterm, documented chronic musculoskeletal pain. Most of the patients treated in these case studies clearly had failed standard traditional care and had chronic progressive musculoskeletal conditions that typically cause debilitating pain as time goes on.[1]

Table 1. Oxford level of evidence backing the use prolotherapy in various conditions[1]

Condition	Oxford level of evidence
Low back pain	1,2
Myofacial pain	1
Osteoarthritis (knee)	1
Tendinopathy	1,3
Chronic Musculoskeletal Pain	3

Ligament Injury	1,3,4

CONCLUSION

Most studies showed that prolotherapy significantly improved pain and physical function over various times of follow-up compared with saline injection control, exercise alone or before treatment. Use of dextrose prolotherapy is supported for treatment of tendinopathies, knee and finger joint OA, and spinal/pelvic pain due to ligament dysfunction. Efficacy in acute pain, as first-line therapy.[2]

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