Utility of Prolotherapy for Upper Extremity Pathology

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Prolotherapy is a method of treatment of painful musculoskeletal conditions whereby a sclerosing agent is injected into an area of tendinosis or osteoarthritis to strengthen and repair painful connective tissue. It is a safe, effective, and relatively inexpensive nonsurgical treatment modality. This article provides a history of prolotherapy, discusses its proposed mechanisms of action, and provides a review of the existing literature on prolotherapy as a treatment for upper extremity pathologies, specifically, hand osteoarthritis, lateral epicondylitis, and rotator cuff disease. *(J Hand Surg Am. 2018;■(■):■−■. Copyright © 2018 by the American Society for Surgery of the Hand. All rights reserved.)*

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Nonsurgical modalities are initially utilized for many pathological conditions about the upper extremity. A variety of therapies exist, including physical rehabilitation, oral medications, and injection composites, all of which result in variable improvement. Although corticosteroids serve as the most common form of injectable therapy given their potent anti-inflammatory properties and ability to relieve pain, other options exist, such as prolotherapy, that utilize alternative pathways to achieve resolution of symptoms.

WHAT IS PROLOTHERAPY?

Prolotherapy is a treatment that involves the injection of sclerosing agents into an area of painful tendinosis or osteoarthritis. The number of studies investigating prolotherapy has multiplied recently, and many of these studies focus on its use in upper extremity pathologies. The first report on musculoskeletal application of prolotherapy was in 1956 when Hackett[1] described his successful experience treating a variety of conditions using sclerosing agents. He coined the term prolotherapy after determining that the treatment resulted in the proliferation of cells to "strengthen the 'veld' of fibrous tissue and bone to stabilize [an] articulation." Shortly after Hackett published his experience with prolotherapy, there were reports documenting several deaths related to the use of zinc sulfate as a sclerosing agent. Since these reports, zinc sulfate has not been used as a sclerosing agent and there have not been any reported deaths from prolotherapy.[2]

INJECTION TECHNIQUE

Many different proliferant or sclerosing agents have been identified and used in studies. Agents typically involve a mixture of hypertonic dextrose (10%−30%), morrhuate sodium, or phenol-glycerine-glucose. Injections are placed into the affected tendon, ligament, or joint and repeat injections are often necessary to stimulate enough of an inflammatory response. Study protocols vary, although they typically involve repeated injections every 2 to 6 weeks over the course of months. Complications of injection are local and parallel other injection therapies. A subset of the population undergoing

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injections experience self-limiting inflammatory flares and regular activity is typically resumed after resolution.[3] Patients are generally asked not to take anti-inflammatory medications because this may interrupt the controlled and targeted inflammatory process. Injections can be given to patients as first-line therapy, but most studies have described the usage of prolotherapy for those with conditions refractory to other nonsurgical care.

MECHANISM OF ACTION

Recent studies have attempted to identify the biological mechanism of pain and functional improvement after injection of sclerosing agents. Although multiple mechanisms have been proposed for the targeted cellular pathways resulting in an inflammatory state including cellular osmotic rupture, chemotactic attraction of inflammatory mediators, or an increase in the antigenicity of host cells, these pathways have not been studied *in vivo*. Regardless of pathway, leukocyte and macrophage infiltration does occur initially with injection of the 3 aforementioned agents.[4]

Ultimately, the inflammatory response may improve pain by reducing inappropriate neovascularization and accompanying neural ingrowth at sites of chronic tendinopathy.[5] However, tendon and/or ligament structural changes may be what promote symptomatic relief. There is evidence to support that injection of sodium morrhuate into rabbit patellar and Achilles tendons increases their diameters through a proliferative injury repair cycle,[6] while injection into rabbit medial collateral ligaments also increase the collagen fibril diameters and strength at the bone-ligament junction.[7] These structural changes may also be the cause of the increase in strength of rat patellar tendons after injection of sodium morrhuate.[8]

The response produced by hyperosmolar dextrose solutions may have some effect on osteoarthritis progression and cartilage regeneration in animal models.[9,10] These studies had small sample sizes; however, the authors suggest that their results are driven by increases in the tissue osmolarity and glucose availability, which stimulate chondrocyte proliferation and subsequent production of extracellular matrices. One human study looked at the chondrogenic effects of hypertonic dextrose injections placed into severely arthritic knees based on pre- and postinjection arthroscopy and biopsies. Although this study was also limited in sample size, the authors saw increases in metabolically active hyaline- and fibrolike cartilage and significant increases in functional scores as measured by the Western Ontario and McMaster Universities Osteoarthritis Index, a patient-reported outcome measure composed of self-reported scores in the domains of pain, stiffness, and physical function.

HAND OSTEOARTHRITIS

The long-term effects of nonsurgical treatment for osteoarthritis of various joints within the hand are poorly understood, although studies with short-term follow-up show variable improvement from corticosteroid or hyaluronate injection and orthoses.[11]

Few studies have evaluated the efficacy of prolotherapy for the treatment of hand osteoarthritis. Reeves and Hassanein[12] conducted a prospective, double-blind randomized controlled trial (RCT) in which 27 subjects received injections of either 10% dextrose with xylocaine or xylocaine in bacteriostatic water for symptomatic carpometacarpal (CMC), proximal interphalangeal, and distal interphalangeal joints. Injections were performed at 0, 2, and 4 months, and outcomes were determined at 6 months. Follow-up was carried through 12 months to ensure that no serious deleterious effects of injection were seen and crossover was allowed for the control group from 6 to 12 months. At 6 months, pain, as measured by visual analog scale (VAS), was improved at rest, movement, and grip in the treatment group compared with controls (mean, 37% vs 18%), and whereas the mean difference in VAS with movement was clinically and statistically significant, the differences at rest and during grip did not reach statistical significance. Average flexion range of motion was significantly different between treatment and control groups as well at 6-month follow-up ($+8^\circ$ vs -8.6°; $P = .003$). Despite these promising results, they represent short-term follow-up of small numbers of patients with high dropout (25%).

Jahangiri et al[13] conducted a double-blind RCT comparing dextrose and corticosteroid injections for first CMC osteoarthritis. Thirty patients received injections of 20% dextrose mixed with lidocaine monthly for 3 months, and 30 patients received 2 months of normal saline injections and 40 mg of methylprednisolone acetate with 2% lidocaine at the third month. Pain with movement as measured by VAS, hand function as measured by the Health Assessment Questionnaire without Disability Index, and pinch strength were compared within and between groups at 1, 2, and 6 months. On average, both groups significantly improved in all categories. At 6 months, the dextrose group had clinically and

statistically significantly lower VAS scores (mean difference, 1.1; $P = .02$) than the corticosteroid group. Mean difference in hand function was also significantly better in the dextrose group (mean difference, 1.0; $P = .01$). Differences in pinch strength were not significant. The authors note that improvements in pain and function may be related to the ability of prolotherapy to stabilize lax tissue, a key feature noted in the development of CMC arthritis.

LATERAL EPICONDYLITIS

Although the term lateral epicondylitis (LE) implies an inflammatory process, LE is degenerative in nature, spurred by repetitive microtrauma leading to an attempt by the body to heal by upregulating local angiogenesis and fibroblast proliferation.[14] Nonsurgical management of LE with nonsteroidal anti-inflammatory medications, corticosteroid injections, or physical therapy leads to symptom resolution in 90% of patients, but a protracted 6- to 12-month course of resolution may be common. Krogh et al[15] conducted a meta-analysis of 17 trials that assessed the efficacy of 8 different injection therapies in the management of lateral epicondylitis, 1 of which was an RCT evaluating prolotherapy. Beyond 8 weeks, corticosteroid injection did not show pain relief over placebo, bolstering the literature that has demonstrated questionable long-term efficacy of glucocorticoid injections and potentially even worse outcomes than placebo at 1 year.[15] That LE is not driven by tissue inflammation but rather by tendinosis speaks to the limited utility of a potent anti-inflammatory such as a glucocorticoid and suggests that therapeutic modalities with alternative mechanisms, such as prolotherapy, may be helpful.

Scarpone et al[16] conducted a double-blind RCT as a pilot to investigate the efficacy of combined dextrose/sodium morrhuate prolotherapy for LE. Twenty-four participants with at least 6 months of refractory LE were randomized to receive injections of either the sclerosing solution or normal saline at 0, 4, and 8 weeks. The experimental group demonstrated significantly better levels of elbow pain at all time points through 1 year and isometric strength testing at final in-person follow up at 16 weeks. Improvements in grip strength were seen in both groups and were not significantly different between groups. There were no complications of treatment other than self-limited postinjection site pain.

Carayannopoulos et al[17] conducted an RCT comparing prolotherapy to corticosteroid injection for the treatment of LE using patient-reported outcomes. Participants were randomized to receive an injection of either a mixed solution of phenol-glycerine-glucose, dextrose, and sodium morrhuate or methylprednisolone at baseline and at 1 month. The prolotherapy group demonstrated statistically and clinically significant improvements in VAS and Disabilities of the Arm, Shoulder, and Hand (DASH) at both 3- and 6-month time points. After corticosteroid injection, there was only statistical and clinical improvement in DASH at 3 months and there were no statistically or clinically significant differences between injection groups. Despite these promising findings, only 17 patients were included in the final analysis.

Rabago et al[18] randomized patients with LE of greater than 3 months' duration and who had failed 1 other form of nonsurgical management into 3 treatment groups, 50% dextrose injections at 1, 4, and 8 weeks; 50% dextrose + 5% sodium morrhuate injections; or watchful waiting. Compared with baseline as well as the watchful-waiting control group, the experimental arms demonstrated clinically and statistically significant improvement in the primary outcome (Patient-Reported Tennis Elbow Evaluation scores) at multiple time points up to 32 weeks. Other outcomes included grip strength and magnetic resonance imaging severity grading, which did not show significant changes except for grip strength in the dextrose-only group. The lack of an injection control group limits the implications of these results.

ROTATOR CUFF DISEASE

Rotator cuff disease ranging from bursitis to full-thickness tears can often be initially treated with glucocorticoid injections, although these injections may result in modest and short-term improvements.

Lee et al[19] conducted a retrospective case-control study of 110 patients with atraumatic rotator cuff disease refractory to 3 months of initial treatment with physical therapy, oral analgesic agents, suprascapular nerve blocks, and/or subacromial injections with triamcinolone. After failure of initial treatments, the control group of 63 patients continued nonsurgical treatment with no formal protocol. The 63 patients in the prolotherapy group received subacromial injections with 20% dextrose and 1% lidocaine at the initial visit and then at 2 weeks, 5 weeks, and every 4 weeks thereafter until 1 of 3 criteria was met. At 1 year, both groups improved in almost all categories measured, but the prolotherapy group demonstrated significantly greater improvements in pain (VAS), functionality (Shoulder Pain and Disability Index

score), active range of motion, and strength of flexion, abduction, and external rotation.[19]

Bertrand et al[20] conducted a double-blind RCT of 73 patients with confirmed supraspinatus pathology with pain of greater than 3 months' duration and randomized them into 1 of 3 groups: injection of 25% dextrose/0.1% lidocaine/saline into the painful entheses; 0.1% lidocaine/saline into the painful enthesis; or the lidocaine/saline mixture superficial to the tendon. Injections were given on presentation and 1 and 2 months after presentation. Physical therapy was prescribed between injections. Although there were reductions in mean VAS in all groups at 9 months (dextrose-enthesis, 2.9 ± 0.6; saline-enthesis, 1.8 ± 0.7; saline-superficial, 1.3 ± 0.6), these showed no statistical difference. Patients in the dextrose-enthesis group were, on average, more satisfied with their treatment than the saline-superficial group, although no significant differences were noted between the dextrose-enthesis and the saline-enthesis groups. No differences were noted in the pre- and posttreatment ultrasound grading of rotator cuff tendinopathy between groups.[20]

SUMMARY

The reviewed studies have shown positive results for several upper extremity conditions treated with prolotherapy. Although the injections have been shown to be safe in all studies since the late 1950s and efficacious in some, most studies have small sample sizes with variable enrolment criteria and the injection solutions and protocols are nonstandardized. Also, not every study utilizes patient-reported outcomes to truly assess the effects of the intervention. There may be a role for prolotherapy given its excellent safety profile and low cost, although further investigation with well-designed study protocols are necessary prior to its widespread use.

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