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Prolotherapy in Chronic Conditions of the Foot and Ankle

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The efficacy of prolotherapy in the foot and ankle, although not a new conservative treatment, is strongly studied in literature but lacks treatment protocol in lower extremity chronic conditions including tendinosis, ligamentous injury, and osteoarthritis. Despite its promise and benefit in some studies, it remains a controversial and underutilized treatment modality. This review looks at the application and limitations of administering prolotherapy in the foot and ankle and the potential benefit in chronic conditions.

Key words: prolotherapy, proliferation, chronic, dextrose proliferant, foot and ankle

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Standard treatment for foot pain, whether acute or chronic, is generally conservative beginning with having the patient wear properly fitting shoes and/or orthotics. This is typically accompanied with NSAIDs or oral corticosteroids with some form of physical therapy. Recalcitrant or recurrent foot conditions may benefit from steroid injections or protein rich plasma injections before surgical intervention is considered.

Prolotherapy, also called proliferation therapy, is the treatment of a tissue with an irritant into a joint space, ligament insertion, or tendon insertion in order to alleviate pain for conditions including osteoarthritis, ligamentous insufficiency, and tendinosis. The therapy by definition includes the injection of growth factors or growth factor stimulants in order to promote tissue repair and growth. Although a novel treatment adjunct, it is not new to the orthopedic or podiatric profession.

History

Prolotherapy is not a new treatment modality. The idea of inducing inflammation of a joint to allow proliferation of fibrous scar tissue in order increase stabilization was brought to the forefront when Hippocrates began practicing it in the fifth century B.C. [1]. He reportedly treated separated shoulders with inflammatory agents to promote axillary scarring.

George S. Hackett, MD a trauma surgeon from Canton, Ohio, coined the term prolotherapy and is considered to be the father of prolotherapy [2]. As he described it, "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

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fibrous tissue and bone to stabilize the articulation and permanently eliminate the disability." [3] Dr. Hackett introduced prolotherapy to Gustav Hemwall, MD in the mid 1950s. Dr. Hemwall continued Dr. Hackett's work after his passing in 1969, and trained the majority of physicians who practiced the technique, over the next 30 years. Hence, the designation Hackett-Hemwall Prolotherapy was born.

Pathophisiology

Although the exact mechanism by which prolotherapy decreases pain and reduces musculoskeletal disability is debated, it has been found historically to induce ligament and tendon hypertrophy and strengthening, stabilize unstable joints, eliminate musculoskeletal pain, and induce musculoskeletal repair via stimulation of growth factors via the inflammatory cascade [4]. Commonly used prolotherapy solutions include dextrose ranging from 5-50% concentration, phenol-glycerine-glucose (P2G) solution, and sodium morruhate solution with more recent solutions including platelet rich plasma, stem cell, and lipoaspirate (Figure 1). Less commonly used solutions include, phenol, tanic acid, and pumice. Dr. Hemwall is credited as the first doctor to use dextrose by itself when Sylnasol, a fatty acid derivative, became unavailable in the 1980s. It is the mainstay and most commonly used agent in prolotherapy today. It is also a safe prolotherapy agent due to its obvious normal presence in blood chemistry and solubility.

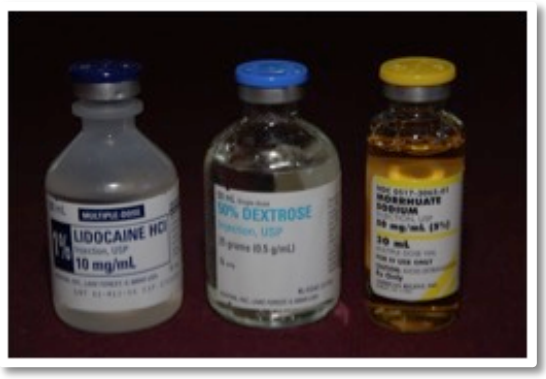

Figure 1. Lidocaine, Dextrose and Morruhate Sodium solutions [5]

Dextrose prolotherapy is thought to work by several different mechanisms including osmotic, inflammatory, and direct. Dextrose injections below a 10% solution directly stimulate proliferation of cells and tissue without causing a histological inflammatory reaction [6]. Normal cells contain approximately 0.1% dextrose; when exposed to higher extracellular concentrations of as little as 0.5%, stimulation of cell proliferation via DNA synthesis, cell protein synthesis, and increase in cell volume begin [7]. The proliferation produces a number of growth factors including platelet-derived growth factor, transforming growth factor-beta, epidermal growth factor, basic fibroblast growth factor, insulin-like growth factor, and connective tissue growth factor. These cytokines are vital and pertinent to growth and repair of collagen and other soft tissues via fibroblasts. Furthermore, numerous studies have shown repair of articular cartilage defects and increase in the size of ligaments and tendon hypertrophy leading to the effect that physicians so desire [8]. When dextrose is injected in greater than 10% solution, it is thought to be causing a hyperosmolar gradient inducing lysis of the cells. This lysis results in an influx of growth factors and inflammatory cells that initiate the sought after wound-healing cascade.

Discussion

Specific protocol of how to administer prolotherapy remains controversial. Proliferant choice varies based on physician along with the interval and frequency of treatment. Although studies have shown that healing responses has been positive across a wide degree of dextrose concentrations, differences in administration still remain [9]. The location of the chronic condition varies from patient to patient along with their response to therapy. Due to these variations, review will be focused upon chronic conditions using solely dextrose prolotherapy in the foot and ankle with outcomes primarily based on the visual analog score.

Achilles Tendinopathy

A few studies have looked at chronic Achilles tendinopathy in patients who underwent dextrose prolotherapy. Lyftogt, for instance, prospectively monitored 169 Achilles over a four-year period after subcutaneous dextrose injection to the midsubstance of the Achilles tendon was performed [10]. He used 0.5-1.0cc of hypertonic dextrose solution ranging from 20-40% with a varying local anesthetic agent. Injections were performed on a weekly basis with an average treatment length of approximately seven weeks. VAS improved from 6.5 to 0.5 with 90% satisfaction after a follow-up period of two years.

Maxwell, on the other hand, used 1.0cc of 25% hyperosmolar dextrose with 2% lignocaineon on 33 Achilles tendons with chronic tendinosis with treatment every six weeks rather than every week [11]. He performed intratendinous injections at hypoechoic areas using ultrasonography and continued treatment until symptoms resolved or lacked improvement with a mean of 4.0 treatments in the study. He used the visual analog score for pain at rest, during daily activity, and during exercise resulting in an improvement of 88%, 84%, and 78% respectively. He followed up 30 of 32 patients with on one patient having remaining moderate pain.

Like Maxwell, Ryan et al performed intratendinous injections on 108 Achilles tendons either at the midportion or insertion using a 25% dextrose solution mixed with local anesthetic [12]. They also used ultrasound to aid them in optimizing the injection and averaged a 5.6 week median interval with a median of five treatments needed. They also used the visual analog score for pain at rest, during daily activity, and during exercise resulting in an improvement of 31%, 41%, and 50% respectively at a 28 month follow-up for patients receiving midportion injections.

Yelland more recently compared prolotherapy injections and eccentric loading exercises, singly and in combination, for painful Achilles tendinosis in 43 patients in a randomized trial [13]. Intratendinous injections were performed weekly for 4-12 treatments of less than 5cc of 20% dextrose and local anesthetic. A 12-week protocol was set in place for the eccentric exercises involving twice daily sets of straight and bent knee sets. Results were compared via VISA-A scores for clinical severity of Achilles tendinopathy; 53% of the eccentric exercise group, 71% of the prolotherapy group, and 64% of the combination group achieved a VISA-A score of at least 90 representing full recovery after 12 months of therapy. However, there was no significant difference over time. Their results show that in painful Achilles tendinosis, prolotherapy and particularly, eccentric loading with prolotherapy, gives more rapid improvement in symptoms than eccentric loading exercises alone.

Hypermobility and Plantar Fasciitis

Ligamentous insufficiency or even hypermobility can be addressed with dextrose as the proliferant in the lower extremity. Tsatsos explored dextrose as a scleroptherapy agent to relieve persistent pain secondary to joint hypermobility due to ligament laxity [1]. He thought that be strengthening tissue structures adjacent to the joint, the joint would be rendered slightly more immobile and thereby decrease the accumulation of inflammatory aggregates. This idea of strengthening the collagen has been explored in rabbit ligaments where the collagen fibrils were found to be more densely packed and of a more uniform size in sclerosed ligaments [14].

Kim et al recently performed a single-blinded, randomized control study on 21 patients who had chronic plantar fasciitis using autologous platelet-rice plasma versus dextrose prolotherapy [15]. Each patient received two injections into the plantar fascia under ultrasound at an interval of 2 weeks with either 2mL of autologous PRP or 2mL of 15% dextrose/lidocaine solution. They used the Foot Functional Index for evaluation of pain, disability, and activity limitation. The results of the study showed the beneficial effects of both dextrose prolotherapy and PRP injection therapies in patients with chronic plantar fasciitis, with improvements in

both pain and function. PRP injection resulted in better outcomes in FFI total scores from baseline during the re-evaluation intervals.

Fullerton used high-resolution ultrasound and magnetic resonance imaging to document tissue repair after a multitude of cases did not respond to previous conservative treatment [16]. In cases of patellar tendon tear, ATFL sprain, and tear of the medial meniscus of the knee, prolotherapy was effective in stimulating tissue growth. Enlargement and fibrosis of ligaments were seen via MRI and showed improved fibrillar patterns and echogenic signaling.

Before Ryan studied prolotherapy on chronic Achilles tendinosis, he reported on its effectiveness for chronic plantar fasciitis using guided ultrasonagraphy on twenty patients [17]. He used 25% dextrose/lidocaine solution at 6-week intervals with a median treatment of three sessions. Visual analog scores improved with a statistical significant difference during rest, daily activities, and during exercise and 16 patients reported good to excellent outcomes.

Osteoarthritis

Although there has been less literature published on dextrose therapy on osteoarthritis of the foot and ankle, benefit and effectiveness has been seen. Some may argue that a large aspect of OA may be secondary to ligament laxity and chronic instability. A 2005 study from the University of Bassel in Switzerland found that 70% to 80% of patients with chronic ankle instability end up with arthritic ankles [18]. Thus by using dextrose prolotherapy on ligamentous and soft tissue structures rather than directly into the joint, one can alleviate pain associated with degenerative joint disease.

Reeves performed a randomized prospective double-blind placebo-controlled study of dextrose prolotherapy for knee osteoarthritis with or without ACL laxity [19]. There were a total of 68 patients analyzed totaling 111 osteoarthritic knees with 25 of them meeting arthrometric criteria of ACL laxity. Patients received three bimonthly injections of 9cc of either 10% dextrose/lidocaine solution or a control solution of lidocaine in bacteriostatic water. Outcome measures included VAS for pain and swelling, frequency of leg buckling, measured flexion, and radiographically measured joint narrowing all of which had statistically significant improvement in the dextrose prolotherapy group. This included osteoarthritic knees with ACL laxity but only at the 12 month follow-up. Reeves suggested that the balance of growth and disrepair factors both in bone and cartilage were in line with optimizing proliferation of human chondrocytes.

Conclusion

Despite its clear benefit and effectiveness in chronic conditions of the foot and ankle, dextrose prolotherapy is an underutilized conservative treatment modality. Strong literature is evident but treatment protocol still varies widely. With its safe application in conditions such as tendinosis, ligamentous injury, and osteoarthritis, it could be used economic yet proactive alternative in high-risk patients.

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