Journal of Prolotherapy International Medical Editorial Board Consensus Statement on the Use of Prolotherapy for Musculoskeletal Pain

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PURPOSE

The purpose of this paper is to explicate the theory, scientific evidence, methods, and applications for the procedure of Prolotherapy in the treatment of musculoskeletal pain. The example of knee osteoarthritis is used as an example as to why Prolotherapy should be used compared to other invasive therapies.

GOAL OF PROLOTHERAPY

The goal of Prolotherapy is the resolution of pain and dysfunction and the optimizing of health by the individual regaining the ability to do activities of daily living and exercise. Once this is achieved, the individual will potentially no longer need medical care for pain and disability. When this goal is not possible, Prolotherapy aims to help improve one's quality of life by diminishing pain and improving mobility, activities of daily living and/or exercise.

INTRODUCTION

Prolotherapy as defined in *Webster's Third New International Dictionary* is "the rehabilitation of an incompetent structure, such as a ligament or tendon, by the induced proliferation of new cells."[1] Most Prolotherapy involves the injection of solutions at the fibro-osseous junctions or entheses, the point at which tendons and ligaments attach to the bone, to induce an inflammatory reaction.[2] This induction of the inflammatory healing cascade initiates the regeneration and repair of the injured tissues in and around the joint, stabilizing and eliminating the sources of most musculoskeletal pain.* Prolotherapy can be an ideal treatment for chronic musculoskeletal pain caused by sprained, injured or torn tendons and/or ligaments in such conditions as joint instability, ligament laxity and tendinopathy including tendinosis; as well as other conditions such as enthesopathies and degenerative osteoarthritis involving the peripheral and spinal joints.

History of Prolotherapy

The theory of Prolotherapy was investigated and practiced as early as the fifth century B.C. by Hippocrates himself. Hippocrates would treat unstable joints by cauterizing the ligaments with a hot metal rod.[3] Although the procedure was rudimentary and experimental, the hypothesis proposed by Hippocrates was that induced inflammation of injured ligaments will lead to self-repair, and that was the one of the first steps towards utilizing the body's own healing mechanism to heal connective tissues. Later in the first century B.C., Celsus, who was a Roman encyclopedist, described the treatment of hydrocele around the testicle via the injections of a Potassium nitrate solution.[4] This provided a prototype of successful treatment of hernias centuries later by Dr. George Heaton in 1832. Dr. Heaton realized that he could tighten the connective tissues around the inguinal ring by injecting them with Quercus Alba solution.[5,6,7] The injection of hernias, varicose veins, and hemorrhoids eventually became known as *Sclerotherapy*, because the injection "sclerosed," or fibrossed, the area.

In 1936, Earl Gedney, DO, an osteopathic surgeon, expanded the technique of sclerotherapy by injecting medial and lateral collateral ligaments of unstable knees

*While pre- and post- ultrasounds and pre- and post- X-rays and biopsy studies in animals have shown that Prolotherapy regenerates damaged musculoskeletal tissues, the mechanism of action of the various types of Prolotherapy is not completely understood. See Histology of Prolotherapy section.

with a solution known as Neoplasmoid. Dr. Gedney found these treatments successful and soon began to treat posterior sacroiliac ligaments with the same solution, also yielding good results.[8] Dr. Gedney published results of this injection therapy to treat the ligamentous pathology involving the knee and lower back including the sacroiliac joint[9]; the annular ligaments of vertebral discs for degenerative disc disease[10, 11]; as well as papers on the use of this type of injection therapy for any hypermobile joint in the body.[12, 13] In 1953 the formation of the first medical organization dedicated to Prolotherapy, then known as sclerotherapy, was the American Osteopathic Association of Sclerotherapy, an affiliate of the American Osteopathic Association. That organization has changed names several times over the years, with its current name the American Osteopathic Association of Prolotherapy Integrative Pain Management and pending name change to the American Osteopathic Association of Prolotherapy Regenerative Medicine.

In 1937, a dentist and facial surgeon at the University of Illinois, Louis Schultz, MD started using Sylnasol (sodium psylliate), a five percent solution of fatty acid, to stabilize temporomandibular joints after he found that the solution could induce fibrogenesis of the injured tissues without causing adverse effects on non-involved tissues.[14, 15] In 1939, a trauma surgeon in Canton, Ohio, George S. Hackett, MD, expanded the concept of tendon pathology and ligament laxity to chronic musculoskeletal pain. He successfully treated various types of spinal conditions in the low back and neck with Sylnasol injections. He was the first to coin the term Prolotherapy. He eventually published a medical book entitled *Ligament and Tendon Relaxation Treated by Prolotherapy* in which he noted "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. To the treatment of proliferating new cells, I have applied the name *prolotherapy* from the word 'proli-' (Latin) meaning offspring; 'proliferate'-to produce new cells in rapid succession."[16] He published numerous papers over the next twenty-five years documenting the success rate of Prolotherapy in the elimination of chronic musculoskeletal pain including results on 1800 patients with chronic low back and noted an 82% cure rate at 12 years after treatment of Prolotherapy.[16-18] Dr. Hackett was also the first to describe in detail the pain referral patterns down the extremities from injured ligaments in the back and neck.[19, 20]

Dr. Hackett's main student and proponent of Prolotherapy was a Chicago surgeon by the name of Gustav A. Hemwall, MD, whom he met in 1955, at an American Medical Association meeting. Dr. Hemwall and Hackett promoted Prolotherapy at various medical meetings and this eventually led to the second medical society devoted to Prolotherapy called The Prolotherapy Association. Upon Dr. Hackett's death in 1969, Dr. Hemwall was the main proponent and teacher of Prolotherapy for the next 30 years, until his death in 1998 at the age of 90. The technique of Prolotherapy that they practiced and taught became known as the Hackett-Hemwall technique of Prolotherapy.[21] The Hackett Hemwall Foundation was set up in their honor to provide high-quality medical treatment to people around the world who would otherwise be unable to afford medical care. The Foundation also promotes research and training to health care professionals in Prolotherapy.[22] Dr. Hemwall eventually found that a simple solution of hypertonic dextrose could be effectively used as the proliferant in the Prolotherapy injections.[21, 22]

While Hackett-Hemwall Prolotherapy is given every three to six weeks to simulate the proliferative phase of healing in the inflammatory cascade, other techniques of Prolotherapy including the west coast and Lyftogt technique of Prolotherapy give treatments up to every week. In more recent years, the solutions for Prolotherapy have expanded to autologous blood products including platelet rich plasma (PRP), and most recently, stem/stromal cells from either bone marrow or adipose (fat).[23] Experimentally cultured stem cells of both bone marrow and adipose have been used successfully to repair various defects including cartilage.[24-28] However FDA regulations prohibit the culture expansion or manipulation of cells in clinical use.[29] Recent protocols have been developed for the use of direct bone marrow and adipose (fat) derived Stem Cell Prolotherapy which do not violate FDA guidelines.[30, 31] Typically, autologous stem cell solutions utilized for Prolotherapy are given monthly to every few months, as needed.*

*The aforementioned are just a few of the great names in Prolotherapy. To read more on these and other physicians including Thomas Dorman, MD, David Shuman, DO, Thomas Ravin, MD, K. Dean Reeves, MD, Paul Goodley, MD, Jeffrey Patterson, MD and others and their role in the history of Prolotherapy please see The History of Prolotherapy by Felix Linetsky, MD in *Prolo Your Sports Injuries Away!* [Beulah Land Press, Oak Park, Illinois. 2001; 25-37.] and A History of the American College of Osteopathic Sclerotherapeutic Pain Management by Donna Alderman, DO in the *Journal of Prolotherapy* [2009;1(4):200-204.]

Epidemiology of Pain

Musculoskeletal pain is in epidemic proportions. In the United States, nine to twenty percent of adults suffer from chronic musculoskeletal pain at any one time.[32, 33] There are currently 15 million individuals who are limited from one daily activity by musculoskeletal pain,[34] and that number is estimated to reach 67 million people by 2030.[35] Additional studies have shown that nearly all chronic pain patients have a substantially reduced health-related quality of life,[36] with 42% unable to work due to pain and 63% unable to engage in routine activities of daily living.[37] The number of knee/hip replacements due to musculoskeletal injuries have increased from 290,700 to 383,500 from 1997 to 2005,[38] and by 2030, the number of these surgical procedures is estimated to increase annually to 572,000/3.48 million.[39] The cost of medical care in treating musculoskeletal pain is astounding, costing Americans in 2004, $849 billion or 7.7% of the gross national product.[40] The anticipated medical costs are expected to double over the next fifteen years.[41]

Musculoskeletal pain can be caused by any type of trauma to the musculoskeletal system, including damage to bones, joints, muscles, tendons, ligaments, bursae, labrum, menisci or nerves. Damage to any of these musculoskeletal components can occur from an acute injury, gradual wear and tear of the tissue, or a combination of both of these factors. The most common cause for musculoskeletal pain, however, is ligament and tendon pathology. The American Academy of Orthopedic Surgeons calculated that ligament and tendon injuries account for 45% of all musculoskeletal injuries in the United States.[42] Due to the difficulty in detecting and diagnosing injuries caused by ligament and tendon pathology via MRI and X-ray, the percentage of musculoskeletal pain caused by ligament/tendon pathology is most likely much higher, especially in chronic pain cases. Ligaments and tendons are soft, collagenous tissue consisting of functional complexes of interdependent aggregations of collagen, elastin, glycoproteins, protein polysaccharides, water, and cells, with the major component of ligaments and tendons being collagen, water, and proteoglycans. Ligaments and tendons are the main connective tissue structures which stabilize and move joints. They often fail to heal completely,[43] because they constantly absorb the brunt force of physical activity, they have a poor blood supply,[44, 45] and the compression, resilience, and durability of articular cartilage decreases with age in correlation to the decrease in water content of the human body, allowing more force to be transmitted to the joint soft tissue structures.[46, 47] Studies have shown that unresolved ligament tears and sprains can completely alter joint mechanics,[48, 49] while ligament laxity and its associated joint instability has been indicated to be the leading cause of spinal and joint degeneration.[50-52] As stated by Dr. George Hackett, "A joint is only as strong as its weakest ligament."[16]

Histology of Prolotherapy

Prolotherapy resolves painful injuries by several mechanisms. Through animal and human research, including biopsy and ultrasound analysis, Prolotherapy injections have been found to induce the repair of soft tissue structures, such as ligament and tendons. Prolotherapy strengthens ligaments and tendons[53, 54] by inducing repair via the stimulation of growth factors via the inflammatory healing cascade.[55-59] An increase of glucose concentration (dextrose) causes an increase in cell protein synthesis, DNA synthesis, cell volume, and proliferation.[60-63] Prolotherapy utilizes the effects of dextrose concentration, as well as other proliferants to stimulate inflammation,[64] which in turn, stimulates ligament size and mass,[65] tendon hypertrophy,[66-68] extracellular matrix,[66-70] fibroblastic proliferation,[66, 68-70] increased ligament-bone junction strength and repair of articular cartilage defects.[71, 72] The increase of extra-cellular glucose concentration from Prolotherapy injections causes cells to proliferate and produce platelet-derived growth factor,[73] transforming growth factor B,[74, 75] epidermal growth factor,[76] fibroblast growth factor[77] insulin-like growth factor,[78] and connective tissue growth factor.[79] These growth factors are pertinent to the repair, health, and growth of tendons, ligaments, and other soft tissue.[77-81] The injected dextrose has been shown to induce healing over a wide range of percent concentrations, protect injured cartilage[71, 72, 82] and cause biological effects by inflammatory and non-inflammatory mechanisms.[66, 67, 71, 72, 82-84] Newer theories and techniques of Prolotherapy have provided additional explanations as to the mechanisms of healing of Prolotherapy including the resolution of neurogenic inflammation.[85, 86]

Types of Prolotherapy

All the various types of Prolotherapy seek to normalize the physiology in injured tissues toward regeneration and renewal. There are many types of Prolotherapy including

Hackett-Hemwall, Subcutaneous, Platelet Rich Plasma, Prolozone™ and stem cell Prolotherapy using either bone marrow or adipose (fat) tissue.

HACKETT-HEMWALL PROLOTHERAPY (DEXTROSE)

Hackett-Hemwall Prolotherapy is a type of Prolotherapy that incorporates the teaching and techniques of George S. Hackett, MD and Gustav A. Hemwall, MD.[87] This technique typically an inflammatory concentration of hypertonic dextrose of 12.5 to 25%.[87, 88] The injections are given into and around the entire painful or injured area. The emphasis is on treating all tender areas and resolving joint instability by treating ligaments and other joint stabilizing structures. Most treatments are given every four to six weeks to allow time for the growth of the new connective tissues. The average person requires three to six visits total.

SUBCUTANEOUS PROLOTHERAPY

Subcutaneous Prolotherapy (also called Neurofascial or Neural Prolotherapy) involves the injection of 5% dextrose into the subcutaneous tissues to induce healing. Research into the healing effects of this type of Prolotherapy originated by a family physician from New Zealand named John Lyftogt.[85] The injections are given just underneath the skin at the location of sensitized peptidergic nerves. These nerves contain transient receptor potential vanilloid receptors (or capsaicin receptors) and are known as TRPV1 nerves. These nerves are sensitized because of trauma, injury or constriction and represent sites of neurogenic inflammation.[85, 88-90] Neurogenic inflammation was first termed "inflammatory neuritis" by Dr. George Hackett in the 1950's.[91-93] Peptidergic sensory nerves are important because they maintain the health and renewal of joint structures, such as ligament and tendons. Injections of 5% dextrose at the sites of sensitized nerves can completely eliminate pain from neurogenic inflammation.[86, 89] The injections are typically given weekly for five to ten visits.

PROLOZONE™

Prolozone is a Prolotherapy technique that utilizes ozone gas, along with other therapeutic substances to stimulate healing and reduce pain in injured soft tissues and joints. The ozone gas is produced when oxygen is exposed to an electric spark via a corona discharge ozone generator. The concentration of ozone in the final gas mixture is between 1-3%.[94] Therapeutic injections of ozone into soft tissue structures, such as muscles, tendons and ligaments as well as arthritic joints for the relieve of pain has been utilized for decades in medical clinics around the world.[95, 96] Various case series have been published documenting the analgesic effect of ozone in osteoarthritis.[97-100] Double-blind randomized-controlled studies have also documented the therapeutic effects of Prolozone in the treatment of low back pain with and without sciatica.[101, 102] As a powerful oxidizing agent, ozone has been found to have pro-inflammatory as well as an anti-inflammatory effect, depending on the concentration utilized. Its proposed mechanisms for tissue repair and regeneration include the stimulating of growth factor production and release.[103-105] Prolozone treatments are typically given weekly for three to 12 treatments, and can be utilized alongside traditional dextrose Prolotherapy.

PLATELET RICH PLASMA (PRP)

PRP involves the injection of concentrated platelets, which release growth factors to stimulate recovery in non-healing soft tissue injuries.[106, 107] PRP contains platelets, wherein reside growth factors that are necessary for healing soft tissues, including platelet-derived growth factor, transforming growth factor and others, which exert their effects on fibroblasts and other immune cells causing their proliferation and thereby accelerating the regeneration of injured tissues.[106, 108, 109] Activated platelets also secrete stromal cell derived factor 1 alpha (SDF-1a) which supports primary adhesion and migration of mesenchymal stem/stromal cells.[110] The preparation consists of an autologous blood collection (blood from the patient), plasma separation (blood is centrifuged), and application of the plasma rich in growth factors (injecting the plasma into the area.)[111] PRP Prolotherapy is typically given every one to two months for one to six visits. High-density platelet rich plasma (HD-PRP) is defined as autologous blood with concentrations of platelets at equal or greater than four (4) times circulating baseline levels,[112] and which increases the important bioactive protein load (growth factors) in a direct correlative fashion.[113] Cell ratios in average circulating whole blood contain only 6% platelets. In true high-density PRP preparations, the concentration achieved is 94%.[114] An average patient platelet count is 250,000 platelets/dl. Four times this is 1 million platelets/dl, which is considered the desired benchmark for "therapeutic PRP."[115]

STEM CELL PROLOTHERAPY

This term describes using autologous adult pluripotent mesenchymal stem cells (MSC's) from an individual's bone marrow or adipose (fat) tissue, as the "proliferating"

solution. An interesting observation made about MSC's is the ability to "home in" and help repair areas of tissue injury.[116] Stem cell Prolotherapy is typically done for more advanced cases of joint degeneration, including osteochondral defects, or where dextrose Prolotherapy and/or PRP Prolotherapy have not resolved a problem. Sources for these cells are a person's own bone marrow or adipose (fat) tissue. With stem cell Prolotherapy a stem cell niche (microenvironment which favors healing) is moved from one tissue in which these niches are abundant (adipose or bone marrow) into one where they are scarce (a non-repairing connective tissue).[117] Stem cells are activated by specific cues within this localized environment to either self replicate or differentiate. From these niches, the tissues, and ultimately the body, can maintain function and replace cells that have been damaged or have died. The niche is a physiologically segregated area of the tissue wherein stem cells are restrained from commitment to extensive proliferation and differentiation and where the stem cells are housed throughout life.[118, 119] Of particular interest is the observation in degenerative diseases, such as osteoarthritis, an individual's adult stem cell frequency and potency may be depleted, with reduced proliferative capacity and ability to differentiate.[120, 121] It has been suggested that addition of these missing stem stem/stromal cell elements might help these degenerative conditions. Studies have demonstrated such improvement with adult stem cell therapy by the successful regeneration of osteoarthritic damage and articular cartilage defects.[122, 123] In 2003, Murphy, et al. reported significant improvement in medial meniscus and cartilage regeneration with autologous stem cell therapy in an animal model. Not only was there evidence of marked regeneration of meniscal tissue, but the usual progressive destruction of articular cartilage, osteophytic remodeling and subchondral sclerosis commonly seen in osteoarthritic disease was reduced in MSC-treated joints compared with controls.[124] In 2008, Centeno et al. reported significant knee cartilage growth and symptom improvement in a human case report using culture expanded autologous MSC's from bone marrow.[125] In 2011, Albano and Alexander used autologous adipose cells as a living bioscaffold and stem cell source to repair a torn patellar tendon.[126] The number of treatments varies depending on condition and prior treatment regime, with clinical protocols in the recent medical literature.[127, 128] Stem cell Prolotherapy is typically given every month to few months.

Lipoaspirate Prolotherapy (ADSC)

While bone marrow has historically been used as a source of MSC's, adipose (fat)-derived stem/stromal cells (AD-SC's) have been shown to have nearly identical fibroblast-like morphology and colonization (CFU-F), immune phenotype, successful rate of isolation, and differentiation capabilities.[129-131] Autologous bone marrow stem cell volume is limited, but adipose tissue represents a large reservoir of stem cells. Research also supports as much as 500 to 1000 times as many mesenchymal and stromal vascular stem-like cells in adipose as compared to bone marrow.[132-134] AD-SC's have been shown, in multiple studies, to improve wound healing and stimulate fibroblast proliferation, migration and collagen secretion, thereby increasing connective tissue tensile strength and healing. Multiple human and animal investigations have clearly demonstrated the in vitro ability of AD-SC's to differentiate into, and repair, musculoskeletal connective tissues including ligament,[135] tendon,[136-138] cartilage,[139-141] disc,[142] muscle,[143-145] nerve tissue,[146-148] bone,[149-151] hematopoietic-supporting stroma,[152-154] to actively participate in tissue homeostasis, regeneration, and wound healing.[155-157] Lipoaspirate Prolotherapy is typically given every four to six weeks.

Bone Marrow Prolotherapy

The primary current use of adult stem cells in orthopaedic therapies are those derived from the bone marrow. In orthopaedic therapies, bone repair and regeneration is driven by the implanted bone marrow MSCs (BMSCs) that either engraft directly into the bone or are recruited from the marrow to the bone.[158-160] Human studies have documented enhanced treatment outcomes for nonunion fractures, avascular necrosis (osteonecrosis) and spinal fusions with the utilization of BMSCs.[161-164] The FDA has already approved the use of bone marrow stems for use in orthopaedics and many companies have products that help separate and thus concentrate the BMSCs from plasma and red blood cells. Centrifugation can concentrate BMSCs up to seven times the normal levels seen in whole marrow without losing cell viability, functionality and ability to osteogenically differentiate.[158, 165-167] Initial research found that using whole bone marrow increased fusion rates in nonunion fractures 28%, but with centrifuged marrow, healing increased to 70%.[158] Others have documented the facilitation of healing with increased BMSC's counts.[161-163] Cell counts in the literature for concentrated marrow have ranged for 16.4×10^6 cells/ml to as high as 2.2×10^9 cells/ml in successful fusions or healings in orthopedic procedures.[160, 161] Numerous publications have demonstrated the benefits

of concentrated bone marrow for the regeneration of various structures of the skeletal system including bone, cartilage, and connective tissues.[168-176] With the except of a few studies, bone marrow derived mesenchymal stem cells have an enhanced potential for chondrogenic differentiation as compared to adipose stem cells.[177-182] Proponents of bone marrow –derived stem cells note the large number of human studies and the fact that bone marrow contains the necessary MSCs and growth factors that are needed for use in orthopedic medicine.[183-187] Typically Bone Marrow Prolotherapy is given every four to eight weeks.

COMMON SIGNS AND SYMPTOMS USED BY PRACTITIONERS AS POSSIBLE INDICATIONS FOR PROLOTHERAPY:

- Laxity of a tested joint, especially compared to the non-painful side
- Distinct tender points at the entheses where tendons or ligaments attach to the bones
- Chronic muscle spasms
- Recurrent swelling or fullness in a joint
- Popping, clicking, grinding, or catching sensations in joints
- Temporary benefit from chiropractic, osteopathic, or self-manipulation that fails to resolve
- Recurrent joint subluxations or dislocations
- Aching, burning or tingling pain or sensation that is referred into an upper or lower extremity

MUSCULOSKELETAL INDICATIONS FOR PROLOTHERAPY:

Prolotherapy is indicated for the following groups of conditions: degenerative arthritis including degenerative joint disease and spondylosis; enthesopathies; ligament injury, including ligament laxity and grade one and two tears; tendinopathy, including tendinosis and tendinitis, and grade one and two tears; joint instability from ligament, labrum or meniscus injury, including congenital conditions including joint hypermobility syndrome and Ehlers-Danlos syndrome; apophysitis and other apophyseal and growth plate injuries, including Osgood-Schlatter disease; other conditions including the pain from complex regional pain syndrome, myofascial pain syndrome, fibromyalgia, post-surgery pain syndrome, and patellofemoral pain syndrome; as well as to augment surgical procedures including ligament and tendon repair (typically grade 3 or complete tears) and fusions.

CONDITIONS SUCCESSFULLY TREATED BY PROLOTHERAPY:

Degenerative Arthritis

Prolotherapy is indicated for the following degenerative arthritis (osteoarthritis or osteoarthrosis) conditions:

- Degenerative Joint Disease involving all peripheral joints including the knees, hips and fingers[188-203]
- Degenerative Spinal Disease including spondylosis, spondylolisthesis and degenerative disc disease[204-209]
- Osteochondral Defects[210-215]

Joint Instability

Prolotherapy is indicated for these ligamentous injuries and other conditions that can cause joint instability and pain:

- Ligament tears and injury[216-220]
- Labral tears and degeneration[221]
- Meniscus tears and degeneration[222, 223]
- Congenital conditions such as joint hypermobility syndrome and Ehlers-Danlos syndrome[224]

Tendinopathy

Prolotherapy is indicated for the following conditions involving tendons and the entheses:

- Tendinopathy[225-231]
- Tendinosis[232-235]
- Tendinitis[236-240]
- Grade one and two tears (partial tears)[241-242]
- Enthesopathies including osteitis pubis and medial tibial stress syndrome[243-245]
- Muscle origin pain and tears[246-248]

Prolotherapy on rare situations can be used for complete tendon tears such as when a patient is not a surgical candidate or has strong desires/reasons not to get surgery. Two case reports show repair of a complete tear/rupture, an Achilles tendon and knee anterior cruciate ligament tear.[249, 250]

OTHER MUSCULOSKELETAL CONDITIONS

Prolotherapy can be successfully used, along with other therapies for the following musculoskeletal conditions:

- Post-surgical pain syndrome[251, 252]
- Myofascial Pain Syndrome[253-256]

- Fibromyalgia[257]
- Complex Regional Pain Syndrome[258]
- Chronic headaches[259-262]
- Radiculopathy[263, 264]
- Autonomic Symptoms, including Barré-Lieou Syndrome[265-268]
- Apophyseal growth plate injuries, including Osgood-Schlatter disease[87, 394]
- Other[269-278]

PROLOTHERAPY AS AN ALTERNATIVE TO NONSTEROIDAL ANTI-INFLAMMATORY MEDICATIONS (NSAIDS), CORTICOSTEROID AND/OR VISCOSUPPLEMENTATION INJECTIONS, PHYSIOTHERAPY, ARTHROSCOPY, JOINT REPLACEMENT AND OTHER TRADITIONAL THERAPIES

Prolotherapy is a viable alternative to pain medications including NSAIDS, physiotherapy and/or cortisone (steroid) injection for the following conditions:

- Tendinitis or bursitis[56, 64, 227]
- Epicondylitis (epicondylosis)[24, 234, 237]
- Plantar fasciitis (fasciosis)[64, 225, 233, 279]
- Tendinopathy (tendinosis or other enthesopathy)[52, 77, 83, 162, 163, 166]
- Ligament injury (tear or laxity)[9, 55, 116, 200, 202, 217]
- Degenerative arthritis (degenerative joint and spinal disease)[57, 93, 205, 206, 209, 277]
- Neuritis[85, 86, 89, 92]
- Temporomandibular Joint Syndrome[14, 15, 197, 280]
- Myofascial Pain Syndrome[64, 83-85, 230, 255, 281]
- Fracture pain[274, 278]

Prolotherapy can be used as alternative to surgery for the following conditions:

- Degenerative arthritis (degenerative joint disease)[93, 109, 188, 189, 194, 211, 212, 221, 222]
- Degenerative spinal arthritis (spondylosis and degenerative disc disease)[10, 11, 17, 277, 282, 283]
- Tendon or ligament tear[114, 241, 242, 284]

PROLOTHERAPY TO ENHANCE SURGICAL OUTCOMES

Prolotherapy can be used to potentially enhance outcomes in the following surgical procedures:

- Tendon repairs[114, 241, 285, 286, 287]
- Fusion[288, 289]
- Ligament repairs[290-292]
- Bone fractures and other lesions[27, 28, 293, 294, 295]
- Osteochondral defects[25, 26, 28, 296-299]

Prolotherapy compared to traditional therapies– The example of knee osteoarthritis

COMPARISON OF PROLOTHERAPY AND OTHER INVASIVE PROCEDURES FOR KNEE OSTEOARTHRITIS, INCLUDING ARTHROSCOPY, STEROID AND HYALURONIC ACID (VISCOSUPPLEMENTATION) INJECTION THERAPY

Musculoskeletal diseases are extremely common and have important consequences to the individual and society. Musculoskeletal diseases according to the World Health Organization are one of the most significant causes of disability around the world. In regard to the burden due to musculoskeletal diseases, osteoarthritis (OA) represents over 50% of the absolute disability-adjusted-life years and that this burden is rapidly growing in both the developed and developing world.[300, 301]

OA is the most common form of arthritis in the world.[302] It is characterized pathologically by both focal loss of articular cartilage and marginal and central new bone formation. OA of the knee, the principal large joint to be affected, results in disabling knee symptoms in an estimated 10% of people older than 55 years, a quarter of whom are severely disabled.[303] The risk of disability attributable to knee OA alone is as great as that due to cardiac disease and greater than that due to any other medical disorder in the elderly.[304] A recent World Health Organization report on the global burden of disease indicates that knee OA is likely to become the fourth most important global cause of disability in women and the eighth most important in men.[305] The annual costs attributable to knee OA are immense.

Knee OA is associated with symptoms of pain and functional disability. Physical disability arising from pain and loss of functional capacity reduces quality of life and increases the risk of further morbidity. When attempts to reduce symptoms by exercise, lifestyle change, and non-steroidal anti-inflammatory drugs fail, more invasive therapies are sought. The current standard of care for unresponsive knee OA by the above methods includes injection of corticosteroids or hyaluronic acid (or its derivatives) into the joint. If these fail, then often arthroscopic or joint replacement procedures are recommended.

INTRAARTICULAR CORTICOSTEROID TREATMENT FOR KNEE OSTEOARTHRITIS GIVES ONLY SHORT TERM PAIN RELIEF (<3 WEEKS)

The effects of intraarticular steroids in knee OA have been assessed in numerous studies. A recent Cochrane Database Systemic Review concluded that the short-term benefit of pain reduction with intraarticular corticosteroids in the treatment of knee OA is well established, however there is a lack of evidence that any benefit occurs after three weeks.[306] Others have confirmed that there is no evidence that intraarticular corticosteroids have any long lasting beneficial effects,[307-309] while some authors note that intraarticular corticosteroids actually accelerate the arthritic process.[310-313]

INTRAARTICULAR HYALURONIC ACID (VISCOSUPPLEMENTATION) FOR KNEE OSTEOARTHRITIS CAN GIVE PAIN RELIEF FOR SEVERAL MONTHS BUT HAS NO LASTING EFFECTS

The role of hyaluronic acid (HA and its derivatives) in pain reduction, functional improvement, and in disease modification has been assessed in over one hundred clinical trials.[314, 315] The overall consensus by various systematic reviews is that although pain relief from HA may be obtained for several months, rather than several weeks as with steroid, this benefit may be offset by a course of three to five weekly injections with the logistical and cost issues that entails.[316, 317] Another concern is that the amount of pain relief on a visual analogue scale (VAS) when overall results are tallied is actually quite small (less than 1 on a 0-10 scale).[318, 319]

There is minimal to no evidence that HA injections have any disease modifying effects.[320] There is little evidence that one HA preparation has any distinct pain-relieving effect over another.[321, 322] The U.S. government agency for healthcare research and quality in 2009 published a clinicians guide for effective health care noting that "viscosupplementation resulted in no meaningful improvement when used as a treatment for osteoarthritis of the knee."[323]

THERE IS STANDARD SCIENTIFIC EVIDENCE THAT ARTHROSCOPIC DEBRIDEMENT OR JOINT LAVAGE FOR KNEE OSTEOARTHRITIS HAS NO BENEFIT

Arthroscopy is the most commonly performed type of orthopedic surgery, and the knee is by far the most common joint on which it is performed. Osteoarthritis of the knee being the main indication for the procedure.[324] Numerous clinical trials including multiple randomized controlled trials comparing arthrocopic debridement to sham surgery and joint lavage, found gold standard evidence that arthroscopic debridement has no benefit for undiscriminated knee osteoarthritis.[325-327] Numerous scientific studies on joint lavage, likewise concluded that joint lavage does not result in a relevant benefit for patients with knee osteoarthritis in terms of pain relief or improvement of function.[328- 330] One study published in the prestigious *New England Journal of Medicine* concluded that "This study provides strong evidence that arthroscopic lavage with or without debridement is not better than a placebo procedure in improving knee pain and function. Indeed, at some points during follow-up objective function was significantly worse in the debridement group then in the placebo…the billions of dollars spent on such procedures annually might be put to better use."[326] The U.S. government agency for healthcare research and quality, as well as the American College of Rheumatology and the American Academy of Orthopedic Surgeons have come out against arthroscopic debridement or joint lavage for knee osteoarthritis. All of them noting that there is no evidence that arthroscopic debridement and joint lavage cures or arrests knee osteoarthritis and does not improve joint function or pain.[331-334]

NO SCIENTIFIC EVIDENCE THAT KNEE ARTHROSCOPY WITH OR WITHOUT MENISCECTOMY AND/OR CHONDROPLASTY CAN SERVE AS A LONG TERM TREATMENT OPTION FOR MECHANICAL KNEE SYMPTOMS FROM KNEE DEGENERATION

Arthroscopic chondroplasty with or without meniscectomy is a common treatment for mechanical knee symptoms including locking, giving way or catching. The term chondroplasty is used for mechanical or thermal reshaping of uneven articular cartilage. The aim is to debride loose chondral flaps and fibrillated articular cartilage to a smoother

surface. Meniscectomy is the surgical removal of all or part of a torn meniscus. Both chondroplasty and meniscectomy involve the removal of knee cartilage or fibrocartilage (menisci) in an attempt to decrease the symptoms caused from impinging osteophytes, articular cartilage and meniscal tears and flaps. Patients who have early-stage degenerative disease and mechanical symptoms of relatively short duration do better with arthroscopic chondroplasty than those who have undergone previous arthroscopy, advanced disease, and chronic, persistent pain. However, no evidence indicates that arthroscopic procedures can predictably serve as a long-term option in the management of the arthritic knee with mechanical symptoms.[335-339] Multiple articles have confirmed that significant rates of cartilage loss are seen in patients post-partial or complete meniscectomy compared to healthy controls.[340, 341] Long-term results following these procedures reveals a high incidence of poor results, degenerative arthritis and ligament laxity.[342, 343] Multiple studies have confirmed that the removal of meniscus tissue from the knee increases joint pressures and instability, leading to an acceleration of the degeneration process.[344-350]

KNEE REPLACEMENT SURGERY (ARTHROPLASTY) IMPROVES LONG TERM QUALITY OF LIFE

Total joint replacement is the most common treatment for advanced osteoarthritis of the knee, with the primary goal of the procedure to improve the patient's quality of life. Many scientific studies and systematic reviews have found that total knee arthroplasties, including minimally invasive techniques, were found to be quite effective in terms of long term improvement in health-related quality-of-life dimensions including pain relief and activities of daily living.[351-357]

PROLOTHERAPY IN THE TREATMENT AND PREVENTION OF KNEE OSTEOARTHRITIS

Scientific evidence is available that Prolotherapy should be utilized in the treatment of knee osteoarthritis. Currently there are no standard treatment options which have been able to arrest the development of osteoarthritis. Progression of joint degeneration often eventually leads to joint replacement.While there are many risk factors for joint degeneration, it is well accepted that the major cause of knee osteoarthritis is ligament dysfunction, especially to the anterior cruciate ligament.[358-364] Being that ligament injury, excess laxity, joint hypermobility, and clinical instability are known to be major causes of osteoarthritis, any treatment which can address restoration of ligament function would help reduce the incidence, pain, dysfunction of osteoarthritis, as well as the need for total joint replacements.

Prolotherapy promotes ligament repair by causing a thickening and tightening of ligaments, as well as the ligament-bone interface (fibro-osseous junction).[365-369] This includes stimulating the repair of the anterior cruciate ligament resulting in increased knee stability.[370-372] Two randomized, prospective, placebo-controlled, double blind clinical trials of dextrose Prolotherapy revealed a statistically significant benefit from the Prolotherapy injections over control. Prolotherapy improved patients quality of life including statistically significant improvement of pain, as well as other quality of life measures including ability of walk and knee instability complaints.[373, 374] Case series in animals and humans have documented improved radiographs and articular cartilage regeneration with Prolotherapy.[375-380] Other studies using Prolotherapy have confirmed that Prolotherapy reduces the need for knee surgeries including meniscectomy and total joint replacement.[381-383]

SUMMARY OF PROLOTHERAPY VERSUS OTHER COMMON INVASIVE PROCEDURES FOR KNEE OSTEOARTHRITIS

Scientific evidence is available that Prolotherapy should be utilized in the treatment of knee osteoarthritis. Osteoarthritis outnumbers all other forms of arthritis combined. The knee being the most commonly involved joint. Knee OA is associated with symptoms of pain and functional disability. Physical disability arising from pain and loss of functional capacity reduces quality of life and increases the risk of further morbidity. When attempts to reduce symptoms by exercise, lifestyle change, and non-steroidal anti-inflammatory drugs fail, more invasive therapies are sought. The current standard of care for unresponsive knee OA by the above methods includes injection of corticosteroids or hyaluronic acid (viscosupplementation) into the joint. If these fail, than often arthroscopic procedures or total joint replacements are recommended.

No common standard therapies used arrest or reverse knee degenerative arthritis. Intraarticular corticosteroids and/or hyaluronic acid (viscosupplementation) have been shown to provide only temporary (less than three months or shorter) pain relief. Long term benefit with these therapies has not been shown. Only total joint replacement has been found to provide long-term pain relief. Arthroscopic knee surgery with or without joint lavage has been found to be

no better than sham (placebo) procedures and is no longer recommended for routine knee osteoarthritis. Arthroscopy with chondroplasty or meniscectomy can reduce symptoms such as knee locking and instability, but long-term accelerate the degenerative process in the knee.

Prolotherapy by promoting ligament repair addresses the major causes of osteoarthritis including ligament injury, excess laxity, joint hypermobility and clinical instability. Studies in Prolotherapy have documented anterior cruciate ligament repair, knee joint stabilization, improvement of radiographic studies, and improved quality of life for patient with knee osteoarthritis. Two randomized, prospective, placebo-controlled, double blind clinical trials of dextrose Prolotherapy revealed a statistically significant benefit from the Prolotherapy injections over control. Prolotherapy improved patients' quality of life including statistically significant improvement of pain, as well as other quality of life measures, including ability to walk and knee instability complaints. Case series in animals and humans have documented improved radiographs and articular cartilage regeneration with Prolotherapy. Other studies using Prolotherapy have confirmed that Prolotherapy reduces the need for knee surgeries including meniscectomy and total joint replacement.

SIDE EFFECTS AND ADVERSE EVENTS WITH PROLOTHERAPY

Prolotherapy, as in all invasive medical procedures, carries risks. While these risks are real, Prolotherapy compared to even anti-inflammatory medications (NSAIDs) or acetaminophen is magnitudes safer, as these medications are responsible for tens of thousands of people dying each year.[384-387] There is a propensity of scientific data that NSAIDs have the propensity to accelerate articular cartilage deterioration in osteoarthritis.[388] The main risks related to Prolotherapy are a result of needle trauma and inadvertinent needle placement. Common side effects at the treatment site include pain, stiffness, bleeding, bruising and swelling. Potential, less common adverse events including nerve, ligament or tendon injury, spinal headache, pneumothorax, nerve damage, spinal cord injury, disc injury, and infection.[389, 390] Prolotherapy spinal injections, as with all spinal injection carries serious risk including injury to the spinal cord and event death, although this is extremely rare.[391-393] Potential allergic and anaphylactic reactions to the agents injected can also occur.

IMPLICATIONS FOR PRACTICE

The practice of Prolotherapy involves years of scientific and clinical research, case studies involving thousands of patients, and treated patients comprising tens of thousands, who attribute to the efficacy of the treatment. The mechanism and application of the treatment have been proven to be sound and safe, producing medically positive results, both short and long term. The theory of Prolotherapy complies with the current medical standards and understanding of human physiology that is involved with the healing of injured musculoskeletal tissues. Positive results have been reported in the scientific medical literature in case series, nonrandomized and randomized for many musculoskeletal conditions, in both osteopathic and allopathic professions.

Clinicians make their recommendations to patients on the basis of their knowledge of human physiology in both health and disease. Since much chronic pain results from the degeneration and injury of musculoskeletal structures such as ligaments, tendons, other soft tissues and joints, and the nerves that support them, then regenerative injection therapy (Prolotherapy) makes physiological sense. Prolotherapy should be one of the preferred therapies when clinicians, including doctors, nurses, and other allied health care professionals, discuss treatment options with patients who suffer from musculoskeletal pain. ■

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