# Prolotherapy (Proliferation Therapy) in the Treatment of TMD

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Proliferation therapy, or "prolotherapy," is also known as regenerative injection therapy (RIT). Since the 1930s, the technique has been used to stabilize injured joints and to relieve joint pain. This article reviews the history and scientific literature regarding prolotherapy and describes the application of the technique to treat injured or unstable temporomandibular joints (TMJ). Alternative medicaments and the likely mechanisms of action are discussed. A brief preliminary summary of a retrospective clinical study of the efficacy of prolotherapy is included. The study shows that prolotherapy can be an effective therapeutic modality that reduces TMJ pain and joint noise in a majority of patients who have reached a plateau with use of an intraoral appliance, physical therapy, and home care.

0886-9634/2304-000$05.00/0, THE JOURNAL OF CRANIOMANDIBULAR PRACTICE,


Manuscript received October 13, 2004; revised manuscript received May 30, 2005; accepted June 24, 2005

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Proliferative injection therapy (prolotherapy), also known as regenerative injection therapy (RIT), has been used to enhance tendon, ligament, and joint healing for over sixty years.[1] The basic practice of prolotherapy involves injections at tendon and ligament insertions with a medicament that stimulates proliferation of fibrous tissue to repair and stabilize the fibro-osseous junction (FOJ).[2,3]

While a review of the scientific literature demonstrates the effectiveness of prolotherapy, some of the articles contain inconsistent, archaic, and potentially misleading terminology.[4,5] Other published material has presented prolotherapy with something less than a scientific perspective, and with hyperbole and inaccurate descriptions and diagrams of anatomy and technique.[6] Only a few of the available references describe prolotherapy for the treatment of temporomandibular dysfunction (TMD).[7-9] This paper reviews the history, scientific basis, and protocols of prolotherapy in an attempt to clarify the terminology and procedures involved when treating the temporomandibular joint (TMJ). A synopsis of a clinical retrospective study of the results of prolotherapy also is included.

Prolotherapy has been referred to as "sclerotherapy," which may be misleading. *Stedman's Medical Dictionary*[10] lists sclerosis as a synonym for induration, which is then

defined as "the process of becoming extremely firm or hard." One example of the contemporary medical use of true sclerotherapy is in the treatment of hemorrhoids.

Referring to prolotherapy as "sclerotherapy" may lead to the mistaken conclusion that prolotherapy causes tissue rigidity and loss of range of joint motion. In contrast, prolotherapy is intended to aid in the biological restoration of joint mobility and strength, while relieving pain.[11] The neuropathic definition of the term "sclerosis" in Stedman's is "hyperplasia of the interstitial fibrous . . . connective tissue," which is a more accurate description of successful prolotherapy.

George Stuart Hackett, M.D., practiced prolotherapy beginning in the 1930s and wrote the book *Ligament and Tendon Relaxation Treated by Prolotherapy*[7] in 1956. Although "relaxation" is not now commonly used to describe pathology, the book's fifth edition with additional material by coauthors Gustav Hemwall, M.D., and Gerald Montgomery, M.D., subheads "ligament and tendon relaxation" as a "skeletal disability" and describes it in the text as incompetent ligament function and loss of joint stability due to strain, sprain, tearing, or degenerative changes. In the presence of such changes, the fibrous tissue in the affected tendons and ligaments elongates and fails to provide physiologic musculoskeletal support.[12,13]

## Joint Physiology

It is important to note that although tendons and ligaments flex, they do not accept significant stretch in the strict meaning of the word. Substantial elongation of fibrous tissue can only be accomplished by rupture of at least a portion of the inelastic collagen fibers within the tissue.[14] Ruptures often occur at the bony interface, which is penetrated at an oblique angle by fibrous strands.[15] Concentration of stress and flexion of the fibrous strands as they emerge from the bone make the FOJ particularly susceptible to rupture. The resultant hypermobility of the injured joint allows excessive strain on the sensory nerves, which results in nociception at the FOJ that is felt as joint pain.[16] One example of this type of injury is in automobile collisions, when shearing forces result from rapid differential acceleration of musculoskeletal components, as large amounts of vehicular kinetic energy are dissipated through the bodies of the vehicular occupants in fractions of a second.[17] Hyperfunction and parafunction also are capable of causing tendon and ligament rupture and elongation, over a longer time span.[18]

Collagen generally heals incompletely and at right angles to the original fibers. Elastin, another tendon and ligament constituent, does not heal at all.[19] Therefore, ligament rupture or elongation is defined as a permanent injury. Continued function on injured joints aggravates and complicates the injury. The temporomandibular joints (TMJs) present a particular concern as it is difficult or impossible to immobilize them, except with surgical intermaxillary fixation bars and wires that hold the teeth in firm contact. Even with the teeth in contact and without chewing, swallowing of saliva happens approximately 600 times each day with over 60 pounds of force applied to the jaw and teeth. Bruxing may increase the force level to 250 pounds.[20] These force and frequency levels can account for the common observation that TMJ injuries worsen with time and continued use of the injured joints.

## History of Prolotherapy

Hackett[21] began performing joint injections in 1939. Literature from the following decades documents similar injection therapy with beneficial results. David Shuman, D.O.,[4] was one early author on the subject, and Earl Gedney, D.D.S., M.D.,[1,22] published articles recounting his many years of experience performing TMJ prolotherapy injections. More recently, joint injection was included in a comprehensive textbook on injection therapy,[23] and prolotherapy has been the subject of multiple lectures and presentations.[24,25]

## Mechanism of Action

Inflammation initiates the biological process of wound healing. Following injury, granulocytes migrate into the injured tissue. Monocytes and macrophages follow the granulocytes to the wound site. Growth factor is released and activates fibroblasts, which produce matrix and new collagen fibrils.[26] Unfortunately, the healing process is often incomplete as the new collagen fibrils grow at right angles to the plane of the injury and do not necessarily align with the original connective tissue. Torn elastin fibers do not heal at all, further compromising the integrity of the zone of healing. Additionally, current therapeutic recommendations include the use of anti-inflammatory medications immediately after an injury. Such medications allay pain and swelling but may diminish the healing response as they reduce inflammation. The result is an insufficiently supported joint that remains painful with normal or even subnormal physical demands. Furthermore, incomplete ligament support leaves the joint hypermobile and prone to reinjury.

Prolotherapy re-initiates the inflammatory process. Histologic studies demonstrate fibroblast proliferation originating in the periosteum following injection of prolotherapy solution. Fibrous tissue in the periosteum con-

tains osteoprogenitor cells (preosteoblasts) that are capable of laying down reparative bone at the FOJ, further strengthening the connective tissue attachment. Periosteal blood flow facilitates repair at the FOJ, which is critical considering the relative avascularity of tendons and ligaments.[27]

Dextrose can cause cell growth by other mechanisms. Research in diabetics has shown that direct exposure to dextrose can cause certain types of cells to grow, and cells in an environment with an osmotic gradient shrink and produce an increase in growth factors.[28] Prolotherapy has been used successfully in many joints in the body and can be used for nearly any tendon or ligament problem in the head or neck.[29] The fact that much of the pain of TMD originates outside the TMJ suggests the usefulness of prolotherapy in treating extracapsular tendon and ligament disorders.

One additional beneficial effect of prolotherapy may be an antibacterial effect. Chlamydia, mycoplasma genitalium, staphylococcus aureus, mycoplasma fermentans/orale, actinobacillus actinomycetemcomitans, and streptococcus mitis have been cultured from the TMJ, and the presence of S. aureus in TMJ synovial fluid was related to TMJ disorder symptoms.[30] Chlamydia trachomatis has been associated with internal TMJ derangements.[31] The osmotic concentration and the bacteriostatic water in the prolotherapy solution may inhibit the growth of, and/or kill, these microorganisms.

## Indications for Prolotherapy

Indications for prolotherapy include: objective evidence of a tendinous or ligamentous injury or disorder of sufficient magnitude to warrant treatment; joint pain with load during function; the patients' desire for treatment and willingness to undergo the discomfort and inconvenience of injection therapy; and the patients' ability and willingness both to complete the injection series as needed and to follow the prescribed home-care instructions.[32-34]

As in the treatment of other joints, TMJ prolotherapy can be advantageous to patients with a temporomandibular disorder (TMD) that is refractory to or has shown only limited success with physical medicine, dietary restrictions, and home care. Prolotherapy also can be advantageous to patients who have not had adequate improvement with oral appliances, or are unable or unwilling to wear such appliances, and who are unsuitable or unwilling candidates for TMJ surgery. Finally, prolotherapy can be used in conjunction with other procedures, such as oral appliance wear, to speed and enhance recovery.

## Contraindications

As with most injection procedures, contraindications include allergy or sensitivity to any of the prolotherapy components, active infection or malignancy in the area to be treated, a healing disorder, hemophilia or any tendency toward excessive bleeding, and inability or unwillingness to cooperate with posttreatment instructions. In addition, parafunctional oral habits and bruxism must be controlled prior to or concurrent with prolotherapy. Treatment of bruxism often involves specific types of intraoral appliances for nocturnal and/or diurnal wear[35] and a home care program that involves jaw position awareness, conscious avoidance of wakeful clenching, and training in proper jaw and tongue position when swallowing.[36]

## Potential Complications

Prolotherapy solutions include such substances as dextrose and local anesthetic agents, which are relatively innocuous when compared to other commonly injected medications. Post injection morbidity following prolotherapy is more likely to result from faulty injection technique than from the proliferant solutions. However, as with the administration of any medicament, the patient must be screened for allergy to any of the injected substances, and the patient must be fully informed as to potential complications of injection therapy. With TMJ prolotherapy, some of these potential complications include discomfort during the procedure, temporary anesthesia that may possibly extend as far as the eye and cause ptosis, and extravasation with external bleeding and/or visible facial bruising. Anxious patients occasionally report dizziness and are at risk of syncope, which can be minimized by supine positioning of the patient during the procedure. Serious side effects with prolotherapy have been documented when spinal cord or thoracic puncture has occurred,[37-39] which is not a significant risk with TMJ injections.

## Routine Side Effects

Introduction of injection fluid into the articular space routinely distracts the condyle and mandible inferiorly and produces a temporary posterior open bite. This change in occlusion in combination with the local anesthetic effect incurs a risk that the patient may unwittingly bite the tongue or buccal mucosa. In those cases when prolotherapy rapidly causes reduction of a displaced disk, the occlusal changes may be permanent. Depending on the extent of such occlusal alterations and the patient's

ability to keep the tongue out of the freeway space, the teeth eventually may settle into solid occlusion through passive eruption,[36] or may require orthodontic and/or prosthodontic correction.[40] In this practitioner's experience, the need for a second phase of treatment to restore occlusion after prolotherapy is rare.

**Postinjection Problems**

Patients must be advised of the routine side effects and potential complications described above. Specific postinjection instructions include restriction to a semisoft diet until the posterior occlusion reestablishes, usually in two to three days, and to avoid rubbing, scratching, or otherwise irritating the anesthetized zone. Eye drops or eye lotion may be necessary in cases of ptosis, for a few hours or until the eyelids regain motility. Speech may be awkward until the anesthetic effect dissipates. Since prolotherapy effects are dependent upon reestablishing a localized inflammation, ice and both prescription and nonprescription anti-inflammatory medications and agents must be avoided for at least several weeks after the injections. Acetaminophen and/or opioid analgesics may be prescribed for postinjection discomfort and to help manage coexistent pain disorders. A signed informed consent form is advisable.

**Prolotherapy Technique**

Patient positioning for TMJ injections generally presents no difficulty. A supine or reclined position is preferred to provide stability of the head and to minimize the risk of syncope. The patient's head is turned as far as comfortably possible toward the opposite side from the injection site. The skin is cleansed and prepared with an alcohol wipe, anatomic landmarks are located, and the injections are administered.

Injection syringes are best limited to three cc maximum if a 30-gauge needle is used. Larger syringes have larger barrel diameters and require excessive injection force, which can make it difficult to determine if the lumen of the needle is obstructed, either by debris or by excessive contact force with periosteum or bone. Five cc syringes may be used with 27-gauge needles, although the larger needle may produce a slight increase in patient discomfort during skin penetration. One-inch needle length is sufficient.

Practitioners vary regarding their precise approaches to articular injections. A common approach is to have the patient close the anterior teeth on a small bite block or two thicknesses of dental cotton rolls to translate the mandibular condyles part way down the glenoid slope of the anterior fossa and to allow access to the superior joint space. The needle penetrates the skin midway between the tragus of the ear and the posterior aspect of the condyle and is directed superiorly and anteriorly toward the apex of the fossa, into the superior joint space, where contact is made with the periosteum. Often, slight momentary resistance is felt as the needle penetrates into the joint capsule. Two cc of prolotherapy solution is slowly injected into the superior joint space. If substantial resistance is encountered, the needle is slightly withdrawn and redirected to ensure that the injection is superficial to, but in contact with, the periosteum. The injection sites are observed for bleeding after needle withdrawal. Bleeding generally is minimal and can be controlled with direct pressure on the site for a few seconds. If the opposite joint is affected, the head is turned to the other side and the identical procedure is repeated on the opposite joint. Injection of the superior joint compartment often improves mandibular range of motion almost immediately. It is possible that introduction of injection fluid into the superior joint space lyses diskal adhesions by the same mechanism as arthrocentesis. The patient is then allowed to rest briefly, a pulse is taken, the patient sits upright when ready and stays until comfort is assured, and the patient is reappointed as necessary and dismissed.

An alternative injection approach is to target the involved ligaments more specifically. Since TMJ disk displacements often are anterior or anteromedial, the elongated posterior diskal ligaments may be treated by injecting one cc of prolotherapy solution immediately posterior to the partially translated condyle. The needle is directed anteriomedially, parallel to the plane of tympanic bone, to avoid penetration into the ear. If the anterior diskal ligaments and superior lateral pterygoid tendon require treatment, the incisal bite stop is removed and the patient is asked to close lightly on the posterior teeth, then one cc of solution is injected anterior to the palpated condyle and directly inferior to glenoid eminence and zygomatic arch. Again, the needle is directed anteromedially, now parallel to the mediolateral contour of the articular slope. Examination of a dry skull may be useful to the practitioner in visualizing the necessary needle angles and depth of penetration. Additional injections of one cc or more of solution may be deposited at other sites to be treated, such as the masseter origins or insertions or the long or short tendons of the temporalis muscles on the coronoid process.

Stylomandibular ligament pain often is treated with anesthetic injections[41] and prolotherapy solution may be used in this area. Injections into the stylomandibular region are from the retromandibular border approximately one centimeter superior to the gonial angle, direct-

ing the needle anteriorly and as near to the medial aspect of the mandibular body as possible, toward the stylomandibular ligament attachment.

Additional sites of tendinous and ligament injury may be identified and treated with prolotherapy. It behooves the practitioner to know the maximum permissible dose of any injected medications and to stay within reasonable limits. A universal recommendation is to inject with the tip of the needle against but not under periosteum.[42]

**Formulations**

Medicaments used in prolotherapy are of four general types: osmotic agents, inflammatory mimetics, chemical irritants, and physical irritants.[43,44] A description of each follows.

Osmotic agents such as 12.5% dextrose produce a hypertonic extracellular environment and cause lysis of the adjacent cell walls. The resultant release of cellular proteins, inflammatory breakdown products of the cell wall, and debris brings macrophages and granulocytes to the area and the desired localized inflammation and fibrous healing begin. Twelve and one-half percent (12.5%) dextrose solution is commonly prepared by diluting 50% dextrose with 1% preservative-free (MPF) lidocaine, and with bacteriostatic water to prevent iatrogenic infection. A common ratio is one part 50% dextrose: two parts 1% lidocaine: one part bacteriostatic water. The mixture can be produced by drawing the three medicaments directly into the injection syringe and shaking before administration, or larger quantities can be prepared, either in the office or by a compounding pharmacy, and stored for later use.

Dextrose is a corn product and should not be used when the patient reports an allergy to corn. Dextrose has been shown to be more effective than lidocaine alone in double-blind analysis,[45] in range of motion analysis,[46] and through subjective patient report.[47]

Sodium morrhuate, derived from the fatty acids in fish oil, is an alternative prolotherapy injection medicament. Sodium morrhuate is believed to convert to, or mimic the activity of, intracellular inflammatory agents that attract macrophages and granulocytes to the injection site.[44]

Chemical irritants such as phenol and physical irritants such as pumice flour attract macrophages and granulocytes, either by cell wall damage or alteration, or by foreign body reaction. However, phenol is caustic and must be handled very carefully, and the introduction of even microscopic foreign bodies such as pumice flour granules into a joint may be a repellent concept to both practitioners and patients.

**Frequency of Injection**

Although some rare patients reach maximum improvement from a single prolotherapy injection appointment, most require multiple appointments. Early prolotherapy practitioners injected at weekly intervals, but there is no evidence that patients received additional benefit from more frequent injections. A common prototypical schedule is to inject at two-week, four-week, and six-week intervals, resulting in four injection appointments over a total of 12 weeks. Fibrous tissue proliferation may continue for as long as several months following prolotherapy injections.

**Follow-up Care**

Patients need to be re-evaluated, typically four to six weeks after the fourth injection appointment and at the practitioner's recommendation after that time, depending the individual patient's response to treatment. Additional prolotherapy injections may be administered if the patient has not reached maximum improvement, but it is appropriate to allow at least several weeks between follow-up appointments to allow the fibrous tissue time to proliferate before administering more injections. Since fibrous tissue proliferation may continue for as long as 18 months after injection therapy, patience on the part of both the practitioner and patient is important. Evaluation of the ultimate success of prolotherapy with any specific patient and of the need for additional injections or for other changes in the treatment plan is best not rushed.

**Retrospective Clinical Study**

Records were examined of 26 consecutive TMD patients who had TMJ pain and TMJ clicking that had been diagnosed as the result of reducing disk displacements. The patients served as their own controls, as each had experienced no improvement with intraoral orthosis therapy, physiotherapeutic care, and home care over the previous three months. The physical condition of each patient, therefore, had plateaued. After discussion of treatment alternatives including no additional treatment, these 26 patients elected to proceed with TMJ prolotherapy. An average of 3.5 injection appointments were completed, ranging from one to seven appointments per patient. Of the 26 studied, TMJ clicking improved in 19 (73%) and disappeared in 12 (46%). Again using a baseline of the 26 studied, TMJ pain improved in 21 (81%) and disappeared in 11 (42%). The author intends to present these numbers in a more detailed article in the near future.

## Summary

Prolotherapy can relieve joint pain and can improve joint stability and range of motion. The encapsulation of the TMJs and the small amounts of relatively innocuous medicament introduced into the TMJs during prolotherapy enhance the safety margin of TMJ injections. The scientific literature and the study synopsis included in this article attest to the efficacy of prolotherapy as a safe and effective procedure for the treatment of TMJ disk displacements, TMJ arthralgia, and associated facial pain.

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