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A Review of the Evidence for Regenerative Injection Therapy

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Regenerative Injection Therapy, also known as prolotherapy, is a relatively simple, minimally invasive intervention for the rebuilding of axial and peripheral joint connective tissue. Various substances, most prominently dextrose, can be utilized, via injection, to stimulate regeneration of injured and/or degenerated ligaments, tendons, and cartilage. This article attempts basic review of the evidence supporting usefulness of this procedure.

Basic science – wound healing cascade

Long established understandings in the basic sciences explain the wound healing cascade as a process stimulated by inflammation.[1,2] In concentrations greater than 10%, dextrose has long been utilized as an osmotic shock agent – a thicker substance to burst some cells in a locale and spill inflammatory eicosanoids and other substances. This simple act signals an immune response that results in a 3-5 day inflammatory cascade, followed by 2-4 weeks of fibroblast activity.[1,3] Fibroblasts are specialized white blood cells that can lay down new, healthy collagen in the area of new injury or RIT injection. This long understood principle of localized inflammation and tissue repair is the basis of how injuries repair on their own. Because many injuries and degenerative processes do not fully heal on their own, prolotherapy has long utilized inflammation and any reasonable means of tissue disruption to re-start the body's own ability to grow new connective tissue.

It is worth emphasizing that tissue disruption is perhaps almost as important as osmotic shock to the stimulation of inflammation and new growth. Acupuncture can involve an ancient technique of "bone-pecking" or "osteopuncture" that involves needle disruption at bony attachments of connective tissue.[4,5,6] Tissue is thus disrupted mechanically by the needle and a healing cascade

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is initiated. This dry needle approach to tissue disruption for tissue regeneration has recently been independently re-discovered by Levon N. Nazarian, MD, Professor of Radiology at Jefferson Medical College, Thomas Jefferson University, in Philadelphia, Pennsylvania.[7,8] During a study using ultrasound to visualize steroid elbow and knee injections, repeated injections on volunteers could not safely be repeated over and over with steroid, and the resultant repeated dry needling was empirically found to cause improvement. A randomized controlled trial is underway. And there are other studies in the medical literature that demonstrate the regeneration stimulating effect of peppering connective tissue with dry needles.[9] This tissue-disruption prolotherapy principle is also the basis for several surgical techniques. Surgeons mechanically abrade rotator cuff tendons to stimulate growth in cases of tendinosis (tendon degeneration and thinning). Surgical techniques for thinning and degeneration of the achilles tendon utilize similar mechanical disruption methods.[10,11,12] Returning from the realm of open surgical techniques to that of injection, an understanding of the mechanism of prolotherapy is enlightened by the fact that injection of any liquid amplifies the tissue disrupting effect of dry needles. Thus, acupuncture physicians in China inject water and other fluids in situations that we may recognize as akin to those in which prolotherapy is used here.[13] One recent study in the journal *Spine*[14] found both dextrose and saline injections more effective than surgery, spinal cord stimulators or multidisciplinary back clinics in treating gradually worsening low back pain of over 14 years duration; the dextrose group was 28% more successful by some parameters, but the "control" group with voluminous saline injection also had statistically very significant results in ameliorating long standing back pain. The large volume of saline injected had tissue disrupting effects to stimulate tissue repair.

Since I am now introducing the basic science foundations of prolotherapy, I will here add that there is basic sciences reasoning for adding nutrients to the fluid used to disrupt tissues and initiate inflammation. Vitamins B-12 and folic acid are rate limiting nutrients for DNA replication[15], and they can thus be injected in this patient's case to supply these key bottle-neck nutrients at the site of stimulated ligament repair. They also both have anti-neuropathic effects, facilitating repair of nerve tissues in the painfully sensitized ligaments and tendons.[16,17,18] Glucosamine sulfate can also reasonably be added to RIT injections to augment collagen synthesis.[19]

Basic science – growth factors

The other major mechanism of prolotherapy action is that of

growth factor recruitment. Growth factors are substances native to the human body that participate in facilitation of tissue growth. One used routinely in the daily practice of medicine is the injection of the growth factor erythropoietin to help patients with anemia to produce more normal red blood cells. Perhaps the most known to the public is human growth hormone, but numerous others have been studied in the basic sciences and in the emerging science of biologic therapies.[20] Numerous large pharmaceutical concerns are in a rush to manufacture recombinant growth factors for use in medicine, but initially more for lucrative markets in regrowth of skin for burn victims and treatment of certain heart diseases. However, simpler, less costly methods already harness growth factors. Blood is a carrier of a more concentrated amount of some of these growth factors, and it is therefore used to fill a knee after arthroscopic knee surgery as a means of stimulating growth of joint tissue. This is a form of prolotherapy via growth factors. A blood patch is routinely applied to inadvertent dural punctures as a way of attracting and concentrating growth factors and speeding repair of the punctured dura. This is a form of prolotherapy via growth factors. But growth factors can also be stimulated and recruited to ligament and other joint tissue by brief exposure to extracellular dextrose, even at less than inflammatory concentrations.[3] This is the growth factor mechanism of action for dextrose prolotherapy, and is highlighted in a series of 3 randomized controlled trials of non-inflammatory joint prolotherapy.[3,21,22]

Animal studies

Prolotherapy has been performed unilaterally on animal ligaments and tendons in studies which have then harvested the treated tissues and compared them to those on the other side. Laboratory testing of the harvested ligaments and tendons found bulk, width, tissue strength, and tissue to bone strength all greatly improved with prolotherapy.[23,24] For example, one of the studies found knee medial collateral ligament mass eventually increased by 47% after inflammatory prolotherapy injection.

Human studies

Three controlled studies of non-inflammatory prolotherapy, mentioned above, attained statistically significant results in knees and finger joints.[3,21,22] Without contradicting the added value of inflammation, these studies were intended to establish the value of growth factor stimulating nutrients (low concentration dextrose) and tissue disruption by fluid.

Eight other studies that I will discuss below utilized inflammatory prolotherapy. They have generally tried to fit into

the dominant research mode of comparing results of testing some injection method against a control somehow presumed to be of no value. Thus injection with an inflammatory substance has been compared to dry needling or injection of saline or anesthetic only. For prolotherapy, like for acupuncture, this method is inherently flawed, as any needling, especially with fluid disruption of tissue, is understood to have therapeutic value. Nevertheless, even with such inherent paradoxical limitations, the studies almost entirely supported the scientific validity of inflammatory prolotherapy. Of course, as with all scientific research, the studies to be considered on their individual merits:

Two low back studies with good coverage of ligaments related to both low back and leg pain revealed an impressive 60% sustained reduction in pain and disability after 12 month follow-up.[25,26] Another study by a rheumatologist inadequately versed in prolotherapy had lesser results and has been criticized for injecting only leg pain related ligaments while excluding leg pain patients from the study.

I mentioned above a study from the journal *Spine*.[14] It drew extensive criticism from within the world of prolotherapy (see attached letters to the editor of *Spine*) for numerous procedural irregularities in the delivery of prolotherapy injections, and, perhaps most importantly, for questioning the value of the inflammatory dextrose effect because of the great value of the saline control injections. However, it was notable that the dextrose injections were nevertheless 28% more effective in certain measurements, and that both the saline and the dextrose injections had magnificent effects in ameliorating low back pain in severe, long-term cases that were documented ahead of time to have been gradually worsening. And, this and other studies that seek injection placebo controls all fail to take into account the growth factor stimulating and tissue proliferating effects of needling, micro-bleeding, and tissue disruption via fluid (and this study used large amounts of fluid – 3 cc per site). Some skeptics have tried to contextualize these results as disproving prolotherapy, though this tact is bankrupt in light of the fact that results in resolution of back pain were excellent.

Three studies with prolotherapy injection of intervertebral discs had statistically significant results to again support the scientific validity of prolotherapy. One pilot study in *The Spine Journal* in 2003 treated patients with prolotherapy immediately after receiving diagnostic discography and had good results after 12 month follow-up.[28] A 2004 study in *Pain Physician* used IDET in a control group, with the prolotherapy group demonstrating superior outcomes.[29] Both used an inflammatory level of dextrose and local anesthetic, together with the sulfur-bearing

nutrients DMSO, glucosamine sulfate, and chondroitin sulfate. A 2006 study in *Pain Physician* with an average of 3.5 discal injections, using just dextrose and local anesthetic, yielded an average of 71% improvement in numeric pain scores.[30]

A 2005 study of puboischial groin muscle tenoperiosteal tears in elite kicking sport athletes appeared in the *Archives of Physical Medicine & Rehabilitation*.[31] Quick and lasting results added to the evidence for dextrose prolotherapy.

A 2005 study in *Pain Physician* by a neurosurgeon on the staff of Mass General had similarly supportive results. This singe blinded, randomized and cross-over study characterized prolotherapy as a "minimally invasive" therapy aimed at periosteal trigger points at sites of enthesopathy. As with most all of the scientific studies, success rates were high, in this case 80%.[32]

Yet another 2005 study that only 3 dextrose prolotherapy reversed cervical ligamentous instability.[33]

Other scientific articles could be discussed here, with a more thorough discussion available in other review articles such as the one in the journal *Biomechanics*, September 2004.[34]

Conclusions

A substantial amount of evidence exists for the use of Regenerative Injection Therapy or prolotherapy. This includes basic science understandings, animal studies and an array of human studies. This literature deserves further study regarding the appropriateness of placebo arms, about injection techniques and solutions utilized in each study, and about the mixing of therapies in some older studies. Those issues are beyond this introductory review. Further discussion of this body of evidence is thus called for.

References:

1 Cockbill S, Wounds: The healing process. Hospital Pharmacist 9: 255-260, October 2002
2 Diegelmann R, Evans M, Wound Healing: An Overview of Acute, Fibrotic and Delayed Healing. Frontiers in Bioscience 9: 283-289, January 2004
3 Reeves KD, Hassanein K, Randomized Prospective Double-blind Placebo-controlled Study of Dextrose Prolotherapy for Knee Osteoarthritis With or Without ACL Laxity. Alternative Therapies 6(2): 68-80, March 2000
4 Lowenkopf A, Osteopuncture. Santa Barbara, CA: Medical Arts Press. 1976
5 Helms J, Acupuncture Energetics: A Clinical Approach for Physicians.

Berkeley: Eastwind Books, 1985
6 Mann F, Acupuncture: The Ancient Chinese Art of Healing and How it Works Scientifically. New York: Vintage Books, 1971
7 Peck P, Ultrasound-guided Percutaneous Needle Therapy Effective for Tennis Elbow. Medscape Medical News, December 5, 2002
8 Healing a Tendon Injury, Ivanhoe Newswire, August 13, 2003
9 Altay T, Gunal I, Ozturk H, Local Injection Treatment for Lateral Epicondylitis. Clinical Orthopedics, 398: 127-130, May 2002
10 Testa V, Capasso G, Benazzo F, Maffulli N, Management of Achilles tendinopathy by ultrasound-guided percutaneous tenotomy, Medicine & Science in Sports & Exercise, 34(4):573-580, April 2002
11 Maffulli N, Testa V, Capasso G, Bifulco G, Binfield PM, Results of percutaneous longitudinal tenotomy for Achilles tendinopathy in middle- and long-distance runners. American Journal of Sports Medicine, 25(6):835-840, November-December 1997
12 Testa V, Capasso G, Maffulli N, Bifulco G, Ultrasound-guided percutaneous longitudinal tenotomy for the management of patellar tendinopathy. Medicine & Science in Sports & Exercise. 31(11):1509-1515, November 1999
13 Shangai College of Traditional Medicine, Acupuncture: A Comprehensive Text, O'Connor J, Bensky D, Editors, Seattle: Eastland Press, 1980
14 Yelland MJ, Del Mar C, Pirozzo S, Schoene ML, Prolotherapy injections for chronic low back pain: a systematic review. Spine. 29(19): 2126-2133, October 1, 2004
15 Leszkowicz A, Keith G, Dirheimer G, Effect of cobalamin derivatives on in vitro enzymatic DNA methylation: methylcobalamin can act as a methyl donor. Biochemistry 30(32):8045-8051, August 1991
16 Yamazaki K, Oda K, Endo C, Kikuchi T, Wakabayashi T, Methylcobalamin (methyl-B12) promotes regeneration of motor nerve terminals degenerating in anterior gracile muscle of gracile axonal dystrophy (GAD) mutant mouse. Neuroscience Letters, 170(1):195-197, March 28, 1994
17 Watanabe T, Kaji R, Oka N, Bara W, Kimura J, Ultra-high dose methylcobalamin promotes nerve regeneration in experimental acrylamide neuropathy. J Neurol Sci 122(2):140-143, April 1994
18 Kuwabara S, Nakazawa R, Azuma N, Suzuki M, Miyajima K, Fukutake T, Hattori T, Intravenous methylcobalamin treatment for uremic and diabetic neuropathy in chronic hemodialysis patients. Internal Medicine, 38(6): 472-475, June 1999
19 Marinelli, R, Adelson, H, The Rose of Naturopathy in Pain Medicine. Weiner's Pain Management: A Practical Guide for Clinicians – Seventh Edition. Boswel, MV, Cole, BE, Editors. Boca Raton: CRC Press, 2005
20 Wang J, Conference Report: Highlights from the North American Spine Society 18th Annual Meeting: Biologic Therapies Take Center Stage. Medscape Orthopaedics & Sports Medicine, 8(1), January 9, 2004
21 Reeves KD, Hassanein K, Long Term Effects of Dextrose Prolotherapy for Anterior Cruciate Ligament Laxity. Alternative Therapies 9(3): 58-62, May 2003
22 Reeves KD, Hassanein K, Randomized, Prospective, Placebo-Controlled Double-Blind Study of Dextrose Prolotherapy for Osteoarthritic Thumb and Finger (DIP, PIP, and Trapeziometacarpal) Joints: Evidence of Clinical Efficacy. Journal of Alternative and Complementary Medicine 6(4): 311-320, May 2000
23 Liu, Y. et al. An in situ study of the influence of a sclerosing solution in rabbit medial collateral ligaments and its junction strength. Connective Tissue Research. 11: 95-102, 1983

24 Maynard J, Pedrini V, Pedrini-Mille A, Romanus B, Ohlerking F. Morphological and biochemical effects of sodium morrhuate on tendons. Journal of Orthopedic Research, 3: 236-248, 1985
25 Ongley MJ, Klein RG, Dorman TA, et al. A new approach to the treatment of chronic low back pain. Lancet 2(8551):143-146, 1987
26 Klein RG, Eek BC, DeLong WB, Mooney V. A randomized double-blind trial of dextrose-glycerin-phenol injections for chronic low back pain. J Spinal Disord 6(1):23-33, 1993
27 Dechow E, Davies RK, Carr AJ, Thompson PW. A randomized, double-blind, placebo-controlled trial of sclerosing injections in patients with chronic low back pain. Rheumatology 1999;38(12):1255-1259.
28 Klein RG, Eek BCJ, O'Neill CW, Elin C, Mooney V, Derby RR. Biochemical injection treatment for discogenic low back pain: a pilot study. The Spine Journal 3, 220-226, 2003
29 Richard Derby, MD, Björn Eek, MD, Sang-Heon Lee, MD, PhD, Kwan Sik Seo, MD, and Byung-Jo Kim, MD, PhD, Comparison of Intradiscal Restorative Injections and Intradiscal Electrothermal Treatment (IDET) in the Treatment of Low Back Pain. Pain Physician, 7 (1): 63-66, 2004
30 Miller, M, Mathews, R, Reeves, KD, Treatment of Painful Advanced Internal Lumbar Disc Derangement With Intradiscal Injection of Hypertonic Dextrose. Pain Physician, 9 (2): 115-121, 2006
31 Topol G, Reeves KD, Hassanein K, Efficacy of Dextrose Prolotherapy in Elite Male Kicking-Sport Athletes With Chronic Groin Pain, Archives of Physical Medicine & Rehabilitation, 86(4): 697-702, 2005
32 Wilkinson H, Injection Therapy for Enthesopathies Causing Axial Spine Pain and "The Failed Back Syndrome:" A Single Blinded, Randomized and Cross-Over Study. Pain Physician, 8: 167-176, 2005
33 Centino, CJ, Elliott, J, Elkins, WL, Freeman, M, Fluoroscopically Guided Cervical Prolotherapy for Instability with Blinded Pre and Post Radiographic Reading. Pain Physician, 8: 67-72, 2005
34 Reeves KD, Sweet Relief. Biomechanics, September 2004: 24-35

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