Prolotherapy and Perineural Injection Treatment

Note several images are from Reeves KD, Lyftogt J Prolotherapy: Regenerative Injection Therapy. In: Waldman SD (ed): Pain Management. Philadelphia; Saunders (Elsevier), 2nd ed; 2011:1027-1044. Images from this handout should not be placed on other web sites without permission from Elsevier.

Prolotherapy

Definition: Prolotherapy is injection with the primary intent of repairing connective tissue (that is, ligament, tendon or cartilage). The term Proli is Latin for “to grow.”

How Does Prolotherapy Work? Dextrose injection (12.5% to 25% concentration) stimulates a brief AA (arachidonic acid) pathway inflammation. AA inflammation is the type of inflammation to which most doctors are referring when they use that word. After an injury, the body uses primarily AA inflammation to try to repair the damage. With prolotherapy there is no significant damage, because there is no stretching or tearing of fibers, but the body still begins a repair process, which allows the structure to become stronger and tighter rather than first becoming weaker and looser.

Why do some people get better quickly with prolotherapy? Healing takes months, but some patients get better quickly. This is likely because dextrose and other solutions have effects on nerves as well. This will be described in the Perineural Injection section below.

What about injecting other solutions than dextrose? There are other solutions that stimulate the AA type of inflammation, such as phenol, and they are also called prolotherapy. However, when cells are removed from the human body and then reinjected, that is “bioregenerative.” The primary goal is still repair but it is by use of tissue from living (biologic) sources. This includes injection of whole blood, stem cell injection and platelet rich plasma injection. There is also a treatment modification available that simulates the effect of Ozone in Dextrose solution (Prolozone). We are not directly injecting Ozone at this time, although we are actively seeking researchers to help them publish persuasive articles in this area and prove effectiveness and cost effectiveness.

Perineural Injection Treatment (PIT), Subcutaneous (PITS) and Deep (PITD)

This technique introduced by John Lyftogt, M.D. in New Zealand has also been called neural prolotherapy (NPT). However the literature does not, as yet, support that growth or proliferation occurs with this treatment. It is for that reason that use of a more generic term has been recommended, instead of prolotherapy. In Australia and New Zealand the umbrella term perineural injection treatment (PIT) appears to be favored by Dr. Lyfogt. PIT is different from other injection methods about nerves because of what is injected and how it is injected. This technique is in the process of rapid refinement and research is underway to learn more about its abilities. The first instructional course was held in November, 2009 so it is a treatment in its relative infancy. Note that this explanation is not intended to favor a particular approach, as both prolotherapy and PIT have merit and, until further research clarification, the need for combining treatments for any particular condition cannot be stated definitively.
Definition of Perineural Injection Treatment (PIT): *Injection close to nerves to restore their normal function.*

**How PIT Works:** There is another type of inflammation that has been recognized, and that is called neurogenic inflammation (N-inflammation). This type of inflammation is produced by certain small sensory nerves that are protein producing (“peptidergic”). These nerves normally produce proteins that can be either healing or damaging. When damaging proteins are produced, that is called neurogenic inflammation. There are many scientific articles published each month on this type of inflammation. Dextrose injection in low concentration (5%) reduces N inflammation. N inflammation does not stimulate AA inflammation like prolotherapy does; the primary intent of PIT is to treat nerves, not ligaments, tendons, or cartilage. The main goal is not to grow new tissue, but to reset nerves to a healthy functioning state.

**Why can’t you take a pill for neurogenic inflammation?** There are a number of medications that calm nerves, but don’t heal them: Gabapentin (Neurontin), Pregabalin (Lyrica) or Duloxetine (Cymbalta). However, the medications that reduce the actual nerve inflammation all over the body affect more than just neuropathic pain. Side effects of these medications have blocked the completion of clinical trials, although medication trials continue. Injection to directly treat the nerves does not affect nerves all over the body, so these side effects are not seen. In addition, there are creams which help reduce nerve inflammation, with mannitol cream particularly well tolerated. Vitamin D cream helps as well but is compounded by the pharmacy and will be more expensive. Dextrose cream helps but is “sticky” on the skin.

**“Bad Nerves”, Nerve-Based Inflammation, and Why Arthritis Meds Don’t Help**

The “Dr. Jekyll and Mr. Hyde” of chronic pain - TRPV-1 Nerves
In the story of Dr. Jekyll and Mr. Hyde, Dr. Jekyll drinks a potion that causes him to switch back and forth between a very good Dr. Jekyll and a very evil Mr. Hyde. In 1997, a very important protein was completely identified to the point it was successfully reproduced (cloned). This protein sits on the surface of 40% or more of your sensory nerves. The nerves it sits on are nerves that can produce protein. These are scientifically called peptidergic (protein producing nerves). What proteins these nerves produce are controlled by channels on their surface. A channel is a pore that can open and close. The channel that appears to be the most important for controlling these protein producing nerves is called the TRPV-1 channel. If this channel is closed, positive ions (cations) are not allowed into the nerve cell and it can’t cause pain. If the channel opens (nerve inflammation state) positive ions (mostly sodium and calcium) flood into the cell, creating pain promptly and causing the cell to behave badly, producing proteins that cause degenerative changes. You will get an idea how fast this causes pain if you put red pepper on your tongue, since that opens those channels on your tongue. The red pepper channel is also another name for the TRPV-1 channel. The ability for your nerves cells to be “bad” or “good” is illustrated by the effects of the potion that the “good” Dr. Jekyll takes to turn into the “bad” Mr. Hyde proteins). We will call the sensory nerves that are controlled by this channel “TRPV-1 nerves.” This whole system of sensory nerves occurs throughout the body, supplying virtually all areas, and is termed the “peptidergic sensory system” because of the ability of these nerves to make proteins (peptides) to affect other structures. For simplicity, we will focus on the nerves that are now thought to be involved the most in chronic pain. We will call these TRPV-1 nerves.
What Happens When TRPV-1 Nerves Behave Badly – Neurogenic Inflammation
When the TRPV-1 channel is “over-active” (up-regulated), the TRPV-1 nerve produces proteins that directly cause pain (Substance P is an important one) and proteins that can cause breakdown in all soft tissue structures (CGRP-1 or calcitonin-gene-related peptide is an important one). These degenerative proteins become directly responsible (through N inflammation) for soft tissue dysfunction in joints and nerve pain like peripheral neuropathy.

Why Anti-Inflammatory Medications Don’t Work For Neurogenic Inflammation
Anti-inflammatory medications target the AA-inflammation and often do so by blocking cyclooxygenase. Blocking cyclooxygenase does not affect the N inflammation pathways. Anti-inflammatory medications have some pain-relieving ability other than just by blocking AA inflammation, so they can be useful, although seldom strikingly useful.

How Do Bad Nerves Affect Other Structures (ie, ligaments, tendons, and cartilage) And Cause Chronic Pain?

Hilton’s Law: TRPV1 nerves connect to all other structures and interconnect with each other.
Hilton’s Law indicates that nerves that cover the skin are joined by nerves from joints, ligaments, and tendons on their way to the spinal cord.

“Switching Road Signs”

How to transport good or bad proteins to ligaments, tendons, joints, nerves
In many spy novels, a trick often used is to switch directional arrow signs to point traffic in the incorrect direction. Sensory nerves (including TRPV-1 nerves) are equally good at conducting (and transporting proteins) both forward and backward along nerves. On the way to the spinal cord there are many branches that come together, not only from the skin, but from other structures. These proteins can easily “have the road sign switched” and transport their proteins backwards along nerve paths and into other structures. Thus, any irritative protein produced by TRPV-1 nerves can have a wide influence on structures in the area.

How to Make A TRPV-1 Nerve Behave Badly, and Why Nerves Under the Skin Are Commonly Affected

“Claustrophobia”
An important quality of TRPV-1 sensory nerves
Animal studies have clearly demonstrated that simply surrounding a nerve around its entire circumference, even without squeezing it, will shut off fast conduction in that nerve, and cause it to behave abnormally. This depiction illustrates how merely touching a nerve on all sides will lead to a swelling reaction. Although the nerve was merely touched, the area can become a point of constriction as the nerve swells on either side of the constriction. Those patients that have heard of Morton’s Neuroma in feet may be interested to find that this is how nerves in the feet swell up and form neuromas.
“Skin Nerves” in humans are very easy to damage and become pain sources...

These figures show how sensory nerves travel along the skin and then suddenly dive through a layer of fascia to make their way between muscles to travel deeper toward the spinal cord. The first figure shows the collarbone (clavicle) and neck of a person from the front and a very important nerve that has three parts that dive through fascia above the collarbone. The second figure shows openings in the fascia to allow the nerve to make its way through more easily. These nerves or the fascia are very easy to damage since they are right on the surface. If the fascia does not work right it can “button hole” the nerve, as seen in the last figure. Because these nerves are so “claustrophobic,” they can quickly begin acting abnormally.

Skin Nerves Are Easy to Keep Irritated By Muscle Contraction, Being Hit, or by Holding Positions (ie: bad posture)
Because muscles are contracting frequently, and because skin nerves are flat and often change direction suddenly to dive between muscle layers, the TRPV-1 nerves from the skin are easily irritated. Also, they are so easy to hit. For example, notice on this picture the location of nerves on the front of the knee. Hitting the knee cap or on the side of the knee cap could irritate these nerves and make them swell, and thus have more difficulty fitting through the hole in the fascia.

TRPV-1 Nerves are not only irritated when they have to penetrate fascia at the skin level, but also when they have to penetrate layers of fascia in other regions.

Nerves must also make their way around muscles, often turning about 180 degrees or more. This figure shows nerves in the neck that have to course behind a muscle in the neck called the sternocleidomastoid. (From the sternum and clavicle to the lower skull area called the mastoid). These include the nerves pictured earlier that penetrate superficial muscle layers, which now need to pass behind the muscle shown.
TRPV-1 Nerves also have to contend with bones and various “tunnels, or passages. Any of these areas can malfunction or be changed in such a way as to “touch” the TRPV-1 nerve.

This figure shows a depiction of a very important nerve for low back pain called the superior cluneal nerve. It passes through a tunnel that is on the top of the pelvis bone but about 1 to 2 inches deep in most people. It can get trapped or squeezed on either side of the tunnel.

How Can The Nerves Be Treated?

1. **TOPICAL CREAM:** Dr. Bertrand in Vancouver published a study in cooperation with Dr. Reeves that examined the effect of mannitol (like the 6 carbon sugar dextrose but with an OH to make it a sugar alcohol). Bertrand H, Kyriazis M, Reeves KD, Lyftogt J, Rabago D; Topical Mannitol Reduces Capsaicin-induced Pain: Results of a Pilot Level, Double-Blind Randomized Controlled Trial. PM&R 2015; 7(11):1111-1117, doi: 1016/j.pmrj.2015.05.002

   Red pepper was placed on the lip to make it burn (opens the TRPV-1 channel, which makes the cell begin producing burning pain). Mannitol cream was placed on one side of the lip and placebo cream on the other in blinded fashion. The mannitol cream reduced the burning sensation faster. This suggests that topical cream is able to have an effect on the TRPV-1 channel to calm it, either directly or indirectly. Recent thought is that this effect is indirect by closing a tandem (nearby) dual pore potassium channel. (Proposed by John Lyftogt, M.D.) The TRPV-1 channel, if open, can cause a variety of pain types. If mannitol is placed over all the correct nerves twice daily, the pain frequently improves. A blinded and controlled clinical trial is underway to officially evaluate the ability of mannitol to decrease nerve pain. The condition chosen is the pain of shingles, which is a pain due to persistent nerve inflammation. Results from this study will be available in 2017.

2. **PERINEURAL INJECTION TREATMENT SUPERFICIAL (PITS).** It has been clinically observed that injection of 5% dextrose or 5% mannitol under the skin is analgesic to nerve pain, usually completely, and within seconds. This is consistent with a rapid effect of dextrose or mannitol on the TRPV1 channel, or on a nearby channel, as this occurs without anesthetic included. This typically needs to be repeated but after several treatments leads to progressive benefit, and according to ultrasound follow up shows evidence of stimulating healing of deeper structures. A study demonstrating that dextrose injected in the epidural space causes analgesia in those with back and leg pain had been completed and published as an abstract, with full study submitted.


3. **PERINEURAL INJECTION TREATMENT DEEP (PITD):** Injection about a nerve in a deeper region where the nerve has to go around objects or through layers called “fascia” is also utilized, as it is at those points that nerve irritation can occur as well. This stretch by fluid, which had been recently found to be better done with dextrose than lidocaine alone, is called hydrodissection.
How Is Perineural Deep Injection Performed?
(example: superior cluneal nerve)

Recall the illustration where the nerve for back pain was trapped. This picture is from an ultrasound scan showing the top of the pelvic bone where the nerve needs to pass over it. The dotted lines are the lines of fascia on either side of the pelvic bone, holding muscles and other structures in place. Under ultrasound guidance, the needle is placed through the fascia, and fluid is injected to stretch the space.

Summary

We suggest you re-read this information. Focus on:

1. The importance of the TRPV-1 channel as the “faucet” that controls whether a nerve causes pain and why it is so important to “turn down the faucet” (down-regulate) the TRPV-1 channel.

2. How the ability of nerves to conduct both directions and their connection with joints and ligaments allows “bad-behaving” nerves to send “breakdown proteins” and “pain proteins” to those structures.

3. Why nerves should not be ignored when treating deeper structures as they are often the underlying cause of damage to those deeper structures.

4. How prolotherapy turns on AA (traditional) inflammation briefly to repair ligament/tendon and turns down N (nerve caused) inflammation to repair nerves.

5. How TRPV-1 nerves responsible for pain can be treated in several different ways, such as topical mannitol, perineural injection treatment superficial (PITS) and perineural injection treatment deep (PITD).

Best regards,

Dr. Reeves