Explanation of

Prolotherapy and Perineural Injection Therapy (Perineural Subcutaneous Injection and Perineural Deep Injection)

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 whose primary intent is to repair 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 nerve 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 "biologic repair injection." 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.

Perineural Injection Therapy (PIT), which includes Perineural Subcutaneous Injection (PSI) and Perineural Deep Injection (PDI)

This technique, introduced by John Lyttogt, 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. The American Academy of Orthopaedic Medicine nomenclature committee recommended perineural subcutaneous injection (PSI) or perineural deep injection (PDI) as simple descriptive terms with easy acronyms. In Australia and New Zealand the umbrella term perineural injection therapy (PIT) appears to be favored. 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 perineural injection have merit

and, until further research clarification the need for combining treatments for any particularly condition cannot be stated definitively.

Definition of Perineural Subcutaneous Injection (PSI): ***Injection close to subcutaneous (under the skin) nerves to restore their normal function.***

How PSI Works: There is another type of inflammation that has been recognized, and that is called neuropathic inflammation. This type of inflammation is produced by special small sensory nerves that are protein producing ("peptidergic"). These nerves normally produce proteins that can be healing or damaging. When produced damaging proteins that is called "neuropathic inflammation" (see below). There are many scientific articles published each month on this type of inflammation. Dextrose injection in low concentration (5%) reduces neuropathic inflammation. This does not stimulate AA inflammation; the primary intent is to treat nerves, not ligaments, tendons, or cartilage. The primary intent is not to grow new tissue.

Why can't you take a pill for neuropathic inflammation? There are no safe oral medications (so far) to treat neuropathic inflammation, because they cause high body temperature in clinical trials. Injection method is safe, however. In addition, there are creams which help reduce neuropathic inflammation (Vitamin D and dextrose cream).

Definition of Perineural Deep Injection (PDI): This is injection about deeper nerves. Although the mechanism of benefit is expected to be nearly identical to perineural subcutaneous injection, there is a tissue stretch that occurs that may have additional effect. This is often done under ultrasound to target an area where a constriction about a nerve is suspected.

"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 some protein-producing (peptidergic) nerve cells. That protein is called a receptor, because it receives information that causes it to change what the nerve cell does. If the receptor is "mellow" (down-regulated), the nerve cell will be very "good" (produce healthy, non-pain producing proteins). If the receptor is "over-active" (up-regulated), then the nerve cell will be very "evil/bad" (produce damaging and pain-producing proteins). Thus, this small protein receptor on the surface of the nerve cell is the "potion" that will make the nerve cell quickly (in seconds) change its character from "very good" to "very bad." This receptor is called TRPV-1 (transient receptor potential vanilloid - Type 1). We will call the sensory nerves that are controlled by this receptor "TRPV-1 nerves." The 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 supply the skin that are now thought to be involved the most in chronic pain. We will call these nerves simply TRPV-1 nerves or "T-nerves."

What Happens When TRPV-1 Nerves Behave Badly – Neuropathic Inflammation

When the TRPV-1 receptor 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). When the

TRPV-1 nerves are producing degenerative proteins that damage other structures, it is called Neuropathic (nerve-caused) Inflammation.

Why Anti-Inflammatory Medications Don't Work For Neuropathic 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**

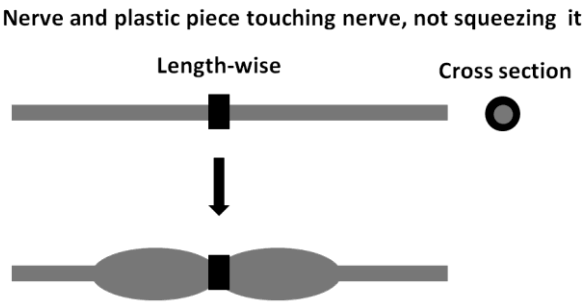
In many spy novels, a trick often used is to switch directional arrow signs to point in the incorrect direction. Sensory nerves (including TRPV-1 nerves) are equally good at conducting (and transporting proteins) both forward and backward along nerves. On the way to the spinal cord there are many branches 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"

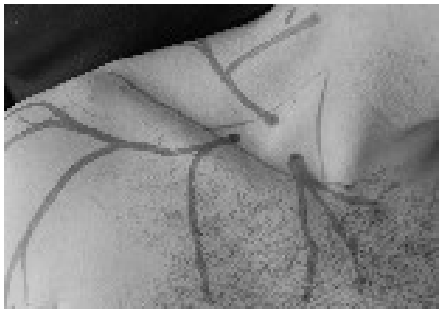
An important quality of TRPV-1 sensory nerves

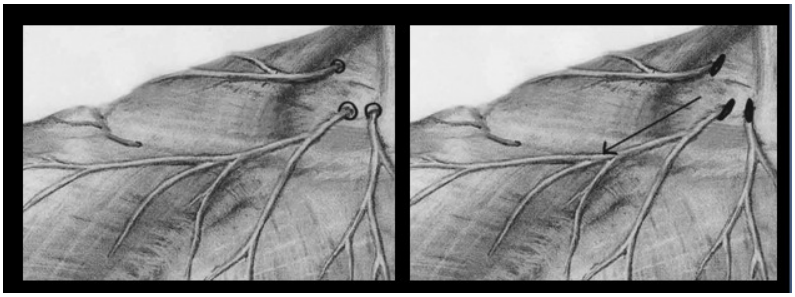
Animal studies have clearly demonstrated that simply surrounding a nerve around its entire circumference, even without squeezing it, will shut off fast conduction in that nerve, and cause it to behave abnormally. This depiction illustrates how merely touching a nerve on all sides will lead to a swelling 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 that this is how nerves in the feet swell up and become neuromas.



Swelling of nerve around the area of nerve touch, which can turn just a "touch" into an area of constriction. Note the nerve has also lost its fast conduction.

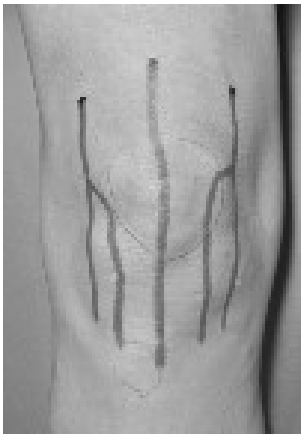
“Skin Nerves” in humans are very easy to damage and become pain sources…





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 begin acting abnormally quickly.

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.



How Can The Nerves Be Treated?

1. TOPICAL CREAM: Early work, as yet unpublished, using stimulation of TRPV-1 receptors on human nerves in the tongue, indicate that Vitamin D or Dextrose downregulate (calm) the TRPV-1 receptor, easing pain. If placed over all the correct nerves twice daily nerves frequently improve. Examination is important because the nerves and their locations are not treated fully by placing the creams or solutions over the area of pain.

2. PERINEURAL SUBCUTANEOUS INJECTION (PSI). It has been clinically observed that injection of dextrose (commonly with 5% dextrose) under the skin is analgesic to nerve pain, usually completely, and within seconds. This is consistent with a rapid block of that TRPV1 receptor 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. The first clinical study proving immediate analgesia from 5% dextrose without anesthetic is about to begin.

3. PERINEURAL DEEP INJECTION (PDI): Injection about a nerve in a deeper region where it 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.

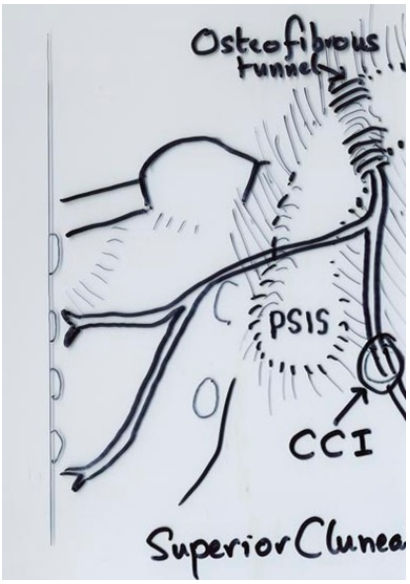
Why Would "Perineural Deep Injection" (PDI) Be Helpful?

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.

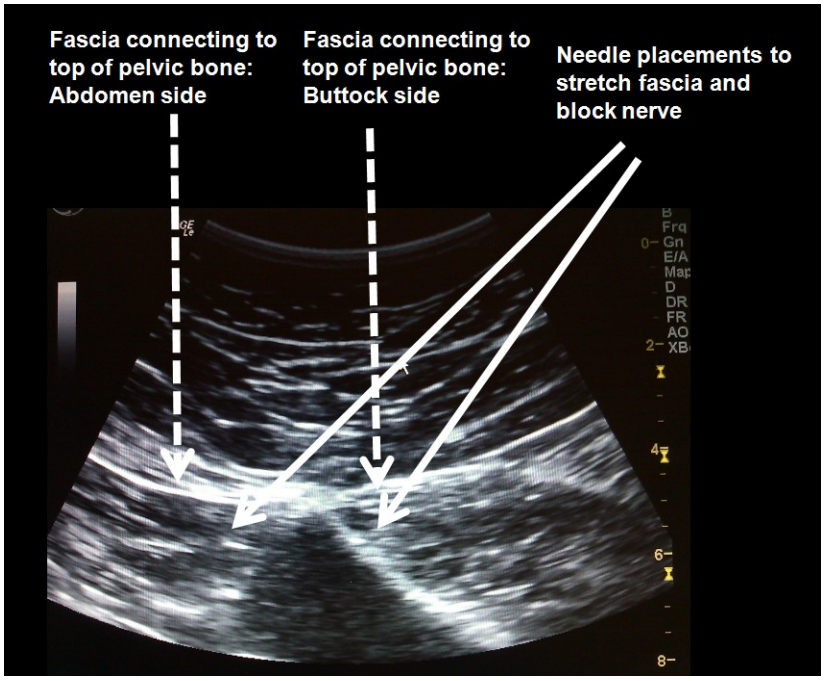
This figure shows a depiction of a very important nerve for low back pain called the superior cluneal nerve. It passes through a tunnel that is on the top of the pelvis bone but about 1 to 2 inches deep in most people. It can get trapped or squeezed on either side of the tunnel.



How 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 receptor 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 receptor.

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 <u>on</u> AA (traditional) inflammation briefly to repair ligament/tendon and turns <u>down</u> N (nerve caused) inflammation to repair nerves.

5. How nerves responsible for pain can be treated in several different ways, such as topical dextrose, perineural subcutaneous injection (PSI) or perineural deep injection (PDI).

Best regards,

Dr. Reeves