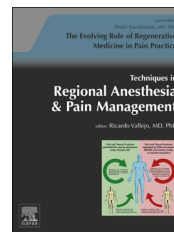


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Peripheral nerve entrapment, hydrodissection, and neural regenerative strategies

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ABSTRACT

Peripheral nerve entrapments are an underrecognized cause of pain and disability. Hydrodissection (perineural deep injections) is one of the techniques that can release the entrapped nerve. Furthermore, discussed are the techniques of neural therapy, neural prolotherapy (perineural injection therapy), and autologous platelet lysate, as well as the use of adipose-derived stem cells.

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Introduction

Peripheral nerve entrapments are common but are often underrecognized sources of pain. An *entrapment neuropathy* is defined as a pressure-induced segmental injury to a peripheral nerve due to an anatomical structure or pathologic process.^{1–3} The defining criteria of an entrapment, according to Kashuk,⁴ include altered transmission because of mechanical irritation from impingement of an anatomical neighbor. Many nerve entrapments occur at areas where the nerve travels through a canal, channel, or tunnel, but they also occur because of trauma and potential scar “strangulation” of the nerve. The nerve has its own blood flow (*vasa nervorum*) as well as accompanying vascular structures. Compression of the nerve, whether intrinsic or extrinsic, can cause damage to the neurovascular structures, leading to ischemia of the nerve. Nerve entrapments can result in clinical symptoms that range from mild discomfort to numbness, paralysis, or incapacitating pain.

Injections have a unique role in the management of peripheral nerve entrapments. Injections can aid in diagnoses, but they can also treat the underlying nerve entrapment, presumably by the anti-inflammatory effect of injected

corticosteroids, hydrodissection of the constricting tissues, and the dilution and flushing out of inflammatory mediators. Precise and atraumatic injection techniques are essential to maximize the informational and treatment value of any nerve injection for peripheral nerve entrapment.

Nerve entrapment

Nerve entrapments may be present in varying degrees, leading to a variety of clinical presentations. Nerves can be entrapped by several mechanisms, including mechanical, which may involve compression, constriction, overstretching, or edema. Entrapment may occur in tunnels (such as carpal tunnel syndrome) (Figure 1), between muscles (such as the axillary nerve) (Figure 2), around blood vessels (such as the occipital nerve) (Figure 3), between bones (such as Morton’s neuroma) (Figure 4), across joints (such as the superficial peroneal nerve) (Figure 5), through fascial penetration sites (such as the anterior cutaneous nerve entrapment syndrome) (Figure 6), or from external compression (such as common peroneal nerve entrapment by a cast) (Figure 7).

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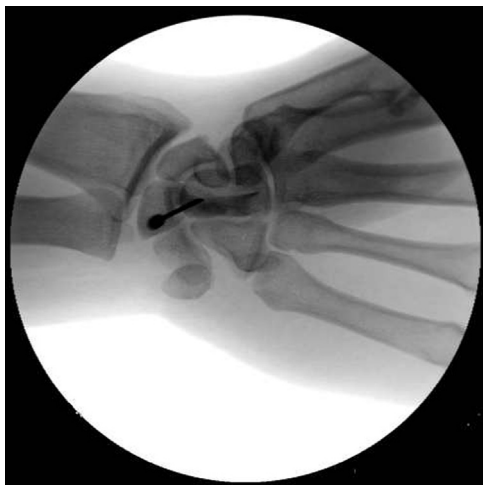


Fig. 1 – Carpal tunnel injection under fluoroscopy, showing contrast in the carpal tunnel. (Image courtesy: Andrea Trescot, MD.)

There are 2 major ways that the fascial penetration point can affect a nerve. Trauma to a nerve would cause edema, which can travel proximal and distal to the injury. When this swelling reaches the fascial penetration points, this can cause a self-strangulation of the nerve and decreased nerve growth factor (NGF) flow. Shearing at the penetration point can also cause entrapment, such as those seen during the distention of the abdomen during pregnancy, causing anterior cutaneous nerve entrapment syndrome.

Peripheral nerve entrapment can lead to or contribute to a wide variety of disorders (Table). In addition, painful conditions with well-described pathology such as complex regional pain syndrome (CRPS) or postherpetic neuralgia likely have a component of nerve entrapment, either as the initiating event (CRPS) or as a consequence of the pathology (postherpetic neuralgia).

The characteristic nerve pain (“neuropathic pain”) is described as burning, shooting, lancinating, or “electric shocks.” There may be allodynia (pain from typically non-painful stimulation) or hyperpathia (longer than expected

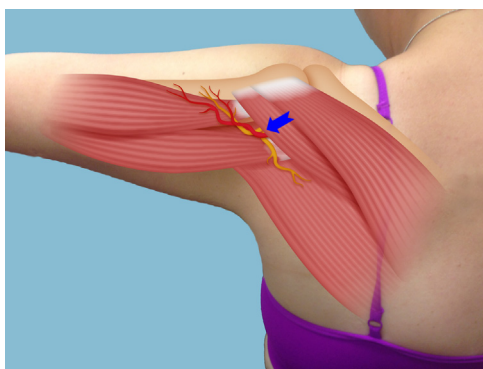


Fig. 2 – Axillary nerve entrapment at the quadrilateral space with the arm in abduction, showing entrapment of the axillary nerve and artery (arrow) by the teres major and teres minor muscles. (Image courtesy: Andrea Trescot, MD.) (Color version of figure is available online.)

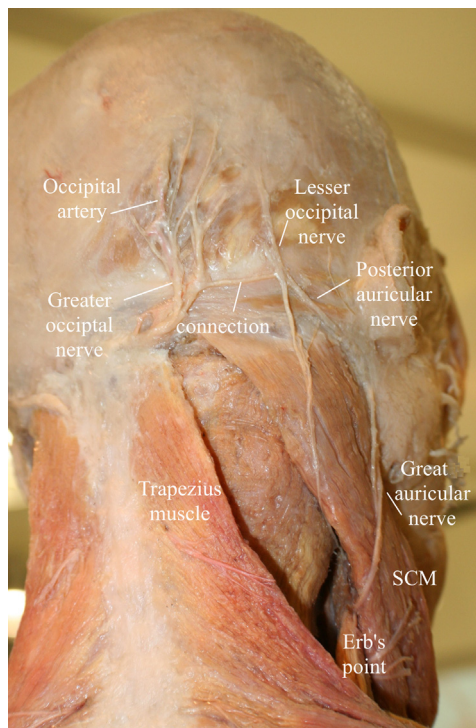


Fig. 3 – Anatomy of the occipital region. (Adapted and modified with permission from Bodies, The Exhibition.) Note the connection of the greater and lesser occipital nerves. (Image courtesy: Andrea Trescot, MD.) (Color version of figure is available online.)

pain from a painful stimulation). This pain often increases over time because of “central sensitization.”

Postoperative nerve entrapments

There are multiple mechanisms by which surgery can cause postoperative nerve entrapments. The pain can occur immediately after surgery because of nerve damage from retractors, scapel, or edema, or it may start weeks or even years after the surgery because of the scar cicatrix that gradually tightens around the nerve.

As an example, pain after total knee replacements can be caused by entrapment of the saphenous (SN) and infrapatellar saphenous (IPS) nerves. The SN, which is composed of sensory fibers from the L3 and L4 nerve roots, branches off the femoral nerve not far below the inguinal ligament (Figure 8), then descends through the anteromedial thigh with the femoral artery and vein to the adductor (Hunter’s) canal. The anatomical variability of the SN, and particularly the IPS,^{5,6} increases distal to the vastoadductor membrane. In most people, 2 or more branches of the SN leave the adductor canal proximal to the joint line, the most anterior of which crosses the knee as the IPS (Figure 9) to innervate the skin below the patella and the anterior-inferior knee capsule. The most posterior branch continues as the distal saphenous (sartorial) nerve, traveling down to the ankle.

The IPS can be traumatized by the medial surgical retractors, and, with the knee in flexion during the procedure, the IPS can be under tension, causing a stretch neurapraxia.⁶

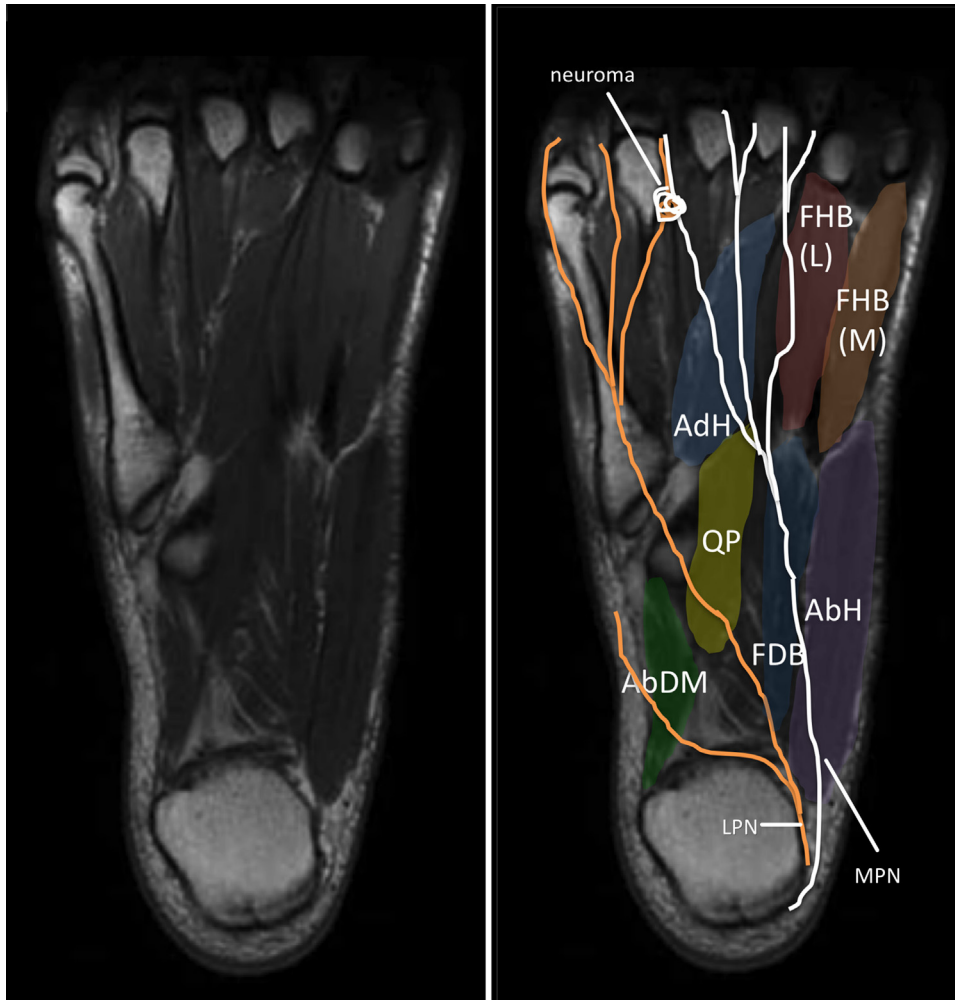


Fig. 4 – Magnetic resonance imaging (MRI) image showing foot muscles and nerves. AdH, adductor hallucis muscle; AbDM, abductor digiti minimi muscle; AbH, abductor hallucis muscle; FDB, flexor digitorum brevis muscle; FHB (L), flexor hallucis brevis (lateral head); FHB (M), flexor hallucis brevis (medial head); QP, quadratus plantae; MPN, medial plantar nerve; LPN, lateral plantar nerve. (Image courtesy: Andrea Trescot, MD.) (Color version of figure is available online.)

Adhesions may also develop between the injured nerve and the adjacent fascial planes, resulting in neuritis.⁶ The patient would present with poorly defined knee pain, perhaps radiating down the proximal shin, with pain on movement or weight bearing, difficulty ambulating, and potentially with allodynia, erythema, and swelling (mimicking an infection). Appropriate diagnosis and treatment are therefore critical to restore function and provide pain relief.

Double crush syndrome and entrapment neuropathy

Upton and McComas observed that 70% of patients with carpal or cubital tunnel syndrome also had electrophysiological evidence of a nerve injury in the neck.⁷ They named the phenomenon the “double crush syndrome,” suggesting that the presence of a more proximal lesion renders the distal nerve particularly vulnerable to compression, with a degree of pain and dysfunction greater than that expected from either entrapment alone. They postulated that compression

on anterograde axoplasmic flow leads to ischemia of the distal segment, later confirmed by other investigators.^{8,9} Double crush syndrome has been observed clinically,¹⁰⁻¹² electrophysiologically,¹³ and experimentally.⁹

As the blood flow and nutrients for the nerve come from its origin in the spinal column,¹⁴ distal nerves tend to be at more risk for injury, owing to limited “resources”; however, because of the length of regeneration needed, proximal peripheral nerve injuries take longer than more distal ones to resolve. Spontaneous recovery is often incomplete and may require up to 2 years or longer.¹⁵

Diabetes mellitus predisposes patients not only to entrapment neuropathies but also to inflammatory neuropathies,^{16,17} thus acting like the “first crush.” This can result in the classic stocking and glove symptom pattern of peripheral neuropathy seen in diabetic patients.^{18,19} Entrapment susceptibility in diabetes seems to be the result of 3 factors as follows:

- (1) increased sorbitol concentration leading to neural swelling,
- (2) abnormal axoplasmic transport,
- (3) and the presence of intraneural collagen-glucose complexes that make the nerve “stiffer” and less compliant.¹⁹



Fig. 5 – Dorsal foot dissection. (Adapted and modified with permission from Bodies, The Exhibition.) White dots, superficial peroneal nerve; green dots, deep peroneal nerve; purple dots, sural nerve. (Image courtesy: Andrea Trescot, MD.) (Color version of figure is available online.)

To continue with the example above, the use of a tourniquet at the proximal thigh during total knee replacement can compress the SN, which can tether the nerve during surgery and act as a proximal entrapment.

- (4) Recent histologic²⁰ and animal²¹ data show that some form of initial nerve trauma is “an important trigger for

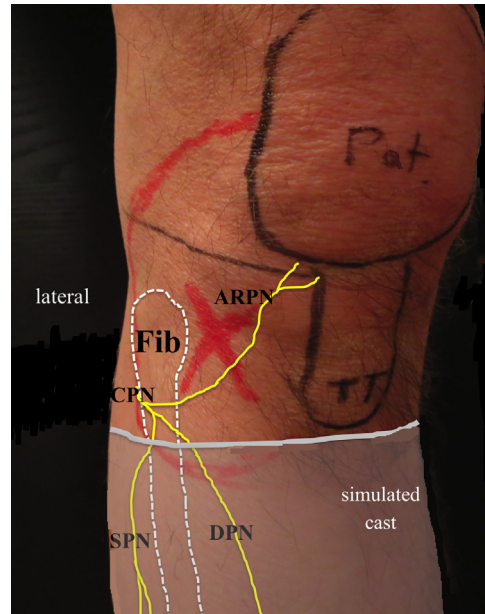


Fig. 7 – Pain pattern of a patient with presumed anterior recurrent peroneal nerve entrapment. Pat = patella; TT = tibial tubercle; Fib = fibula; CPN = common peroneal nerve; SPN = superficial peroneal nerve; DPN = deep peroneal nerve; ARP = anterior recurrent peroneal nerve; X = site of tenderness. (Image courtesy: of Andrea Trescot, MD.) (Color version of figure is available online.)

the cascade of events leading to CRPS.”²² The distinction between the pathogenesis of CRPS-I and that of CRPS-II, therefore, is a matter of degree and not mechanism.²³

Once one gains the understanding of the critical neuroanatomy as well as the ultrasound skills required to target specific nerves, there are several regenerative technologies that can be used with great success in some patients



Fig. 6 – Abdominal wall dissection. (Dissection courtesy: Gabor Balsa, MD, Semmelweis University, Laboratory for Applied and Clinical Anatomy, Budapest, Hungary; Image courtesy: Andrea Trescot, MD.) (Color version of figure is available online.)

Table – Disorders caused by peripheral nerve entrapments.

Headaches	Face pain	Neck pain	Shoulder pain
Ear pain	Jaw pain	Chest wall pain	Abdominal wall pain
Pelvic pain	Hip pain	Knee pain	Foot pain

with peripheral nerve entrapment neuropathies and nerve injury.

Treatments

Neural therapy

Neural therapy was originally described in 1989 for treatment of superficial scars. Local anesthetic, sometimes with small doses of steroids, is injected subdermally to separate the tissue planes, creating a hydrodissection of the tissues (Figure 10). The treatment of scars that tether the skin to the underlying fascia, as well as the treatment of the entrapment of the terminal branches of cutaneous nerves, is not a panacea, but may offer relief to a group of patients who have not been able to find relief elsewhere.²⁴

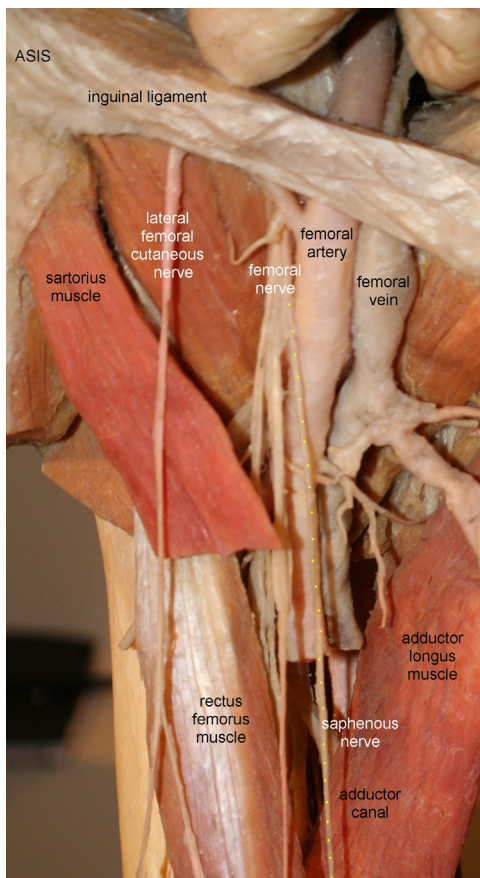


Fig. 8 – Dissection of the anterior thigh and groin. (Adapted and modified with permission from Bodies, The Exhibition.) (Image courtesy: Andrea Trescot, MD.) (Color version of figure is available online.)

Hydrodissection

Hydrodissection, also known as *perineural deep injection*, is a technique of injecting volume into scars or fascia to release entrapped nerves. The nerves are supposed to move smoothly over the fascia, but entrapment of these nerves is similar to adhesions in the epidural space, tethering the cutaneous and deep nerves and causing pain and autonomic dysfunction.

The technique of hydrodissection requires both the skill of the identification of nerves under ultrasound (US) as well as the safe and accurate manipulation of the US-guided needle. The goal is to place the needle tip on each side of the nerve (perineural) but not inside the nerve (intra-neural).

The nerve that is entrapped may appear “hour-glass” shaped (Figure 11), or thickened (Figure 12). After a sterile prep and subcutaneous infiltration of local anesthetic, the nerve is first identified in cross-section, and the needle advanced to the perineural space from an out-of-plane approach (Figure 13). Small aliquots of fluid can help to identify the appropriate fascial plane, which is visualized as an expanding collection of hypochoic fluid around the nerve, in a “donut” shape. The US probe is then turned 90° to show the nerve in a longitudinal view, and most of the

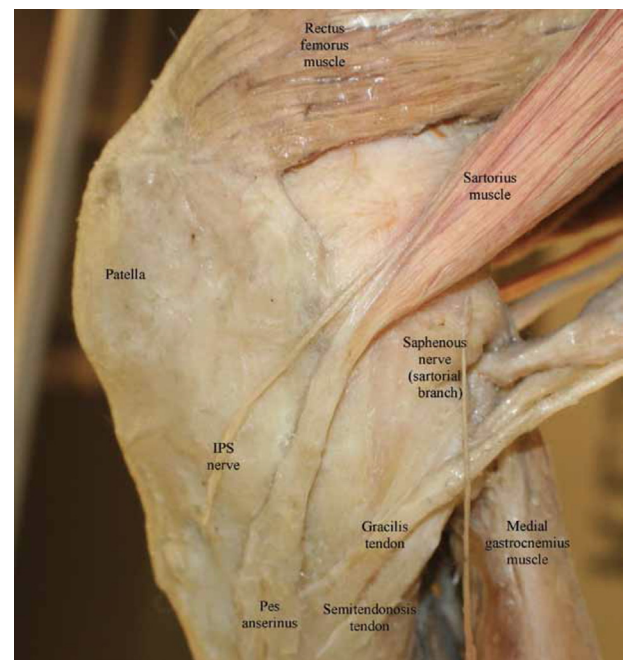


Fig. 9 – Anterior knee dissection. (Adapted and modified with permission from Bodies, The Exhibition.) (Image courtesy: Andrea Trescot, MD.) (Color version of figure is available online.)



Fig. 10 – Subcutaneous hydrodissection of a superficial scar (neural therapy). (Image courtesy: Andrea Trescot, MD.) (Color version of figure is available online.)

injection is then completed with the needle now in-plane (Figure 14). The fluid is injected slowly, watching the careful dissection of the tissues by the fluid. Often a “pop” is felt with the fingers of the palpating hand, and the patient reports an instant relief of pain.

Several warnings are of note. Intraneural injections can result in severe nerve damage and must be avoided. Expansion of the nerve diameter during injection (seen on cross-section) may be an indication of intraneural injection. The nerve should usually be seen moving away from the needle during injection, pushed away by the fluid; the observation of the nerve moving toward the needle might represent an intraneural injection. Large volumes, especially without visible run-off, may result in further entrapment of the nerve; volumes of mL (for small nerves) to mL (for larger nerves or regions) of saline, local anesthetic, or D5W should be adequate.

One of the hydrodissection nerve releases that have been described is the *median nerve*. Malone et al²⁵ described using the US to direct needle placement in the wrist. They

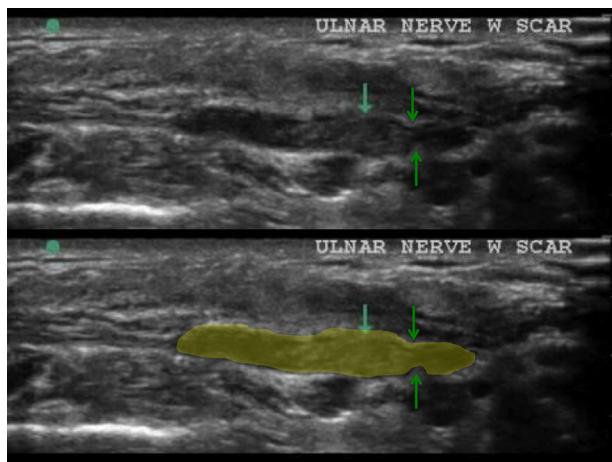


Fig. 11 – Longitudinal ultrasound image showing scarring of the ulnar nerve, with an “hour-glass” shape. (Image courtesy: Michael Brown, MD.) (Color version of figure is available online.)

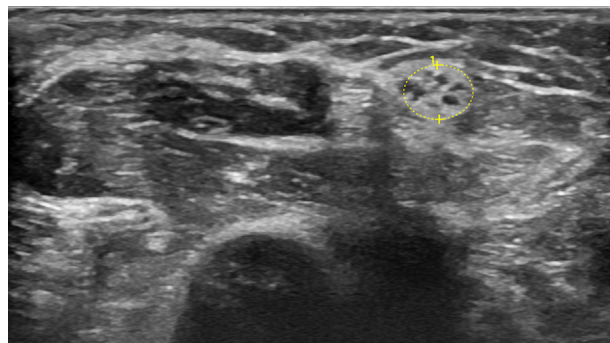


Fig. 12 – Cross-sectional ultrasound image showing thickening of the nerve. (Image courtesy: Michael Brown, MD.) (Color version of figure is available online.)

described injecting 11 mL of hydrodissection fluid (9 mL of normal saline, 1 mL of 1% lidocaine, and 1 mL of 40 mg/mL triamcinolone) deep to the flexor retinaculum via a 20-gauge needle, using the jet of fluid to carefully separate the median nerve from the deep surface of the retinaculum. They then inserted the needle perpendicular to the skin about 150 perforations of the flexor retinaculum, using US to confirm that the needle did not contact the median nerve. These authors felt that this technique was a viable intermediate treatment between conservative measures and open release. Of the 44 wrists treated, 19 noted excellent relief at the initial follow-up (4 days) and at 24 months, 9 wrists with initial excellent relief but only fair relief at follow-up, 5 wrists with fair short- and long-term relief, 6 lost to follow-up, and 5 complete failures.

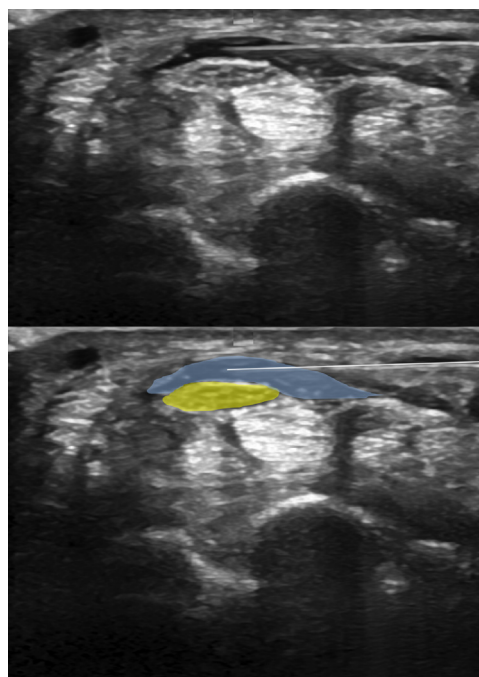


Fig. 13 – Ultrasound hydrodissection of the nerve in cross-section. (Image courtesy: Michael Brown, MD.) (Color version of figure is available online.)

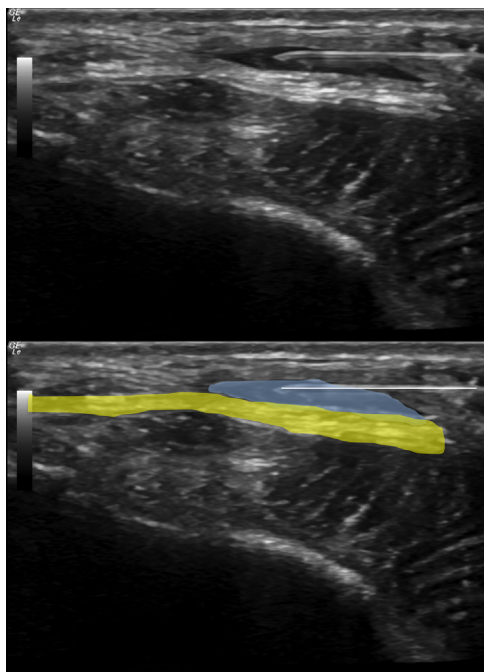


Fig. 14 – Ultrasound hydrodissection of the nerve in longitudinal view. (Image courtesy: Michael Brown, MD.) (Color version of figure is available online.)

Other nerve hydrodissection that have been reported include superficial radial, radial, ulnar, femoral, saphenous, peroneal, posterior tibial, plantar, and ilioinguinal or iliohypogastric nerves.²⁶

Perineural injection therapy or neural prolotherapy

Ligaments, tendons, and joints have transient receptor potential vanilloid-Type 1 (TRPV-1)-sensitive C fiber receptors.²⁷ When the TRPV-1 receptor is “over-active” (up-regulated), the TRPV-1 nerve produces proteins that directly cause pain, including substance P and calcitonin gene-related peptide. When the TRPV-1 nerves (also known as “peptiergic” nerves) produce degenerative proteins that damage other structures, it is called *neuropathic* (nerve-caused) *inflammation*. “The participation of the nervous system in inflammatory reactions was suggested over a century ago, yet nervous elements as potentially important contributors to inflammatory mechanisms has been largely ignored for a long time.”²⁸

Lyftogt described using an injection of dextrose 5% in sterile water (D5W) around a variety of nerves.²⁹ The mechanism that he proposed³⁰ was that dextrose seemed to bind to presynaptic calcium channels and inhibit the release of substance P and calcitonin gene-related peptide, thus having a beneficial effect of decreasing neurogenic inflammation. This was thought to have neurotrophic effects on growth factors that ultimately might provide a mechanism for subsequent nerve repair and decreased pain. Low concentration (5%) dextrose injections reduce neuropathic inflammation.

This suggestion has led a number of physicians skilled in ultrasonography to use US to isolate nerves, and to use saline or D5W to hydrodistend and hydrodissect tissues around the

perineural region, mechanically decompressing the nerve. The use of D5W delivers dextrose to the perineural soft tissues, which may aid recovery of the nerve after decompression. Di Fabio and Pybus³¹ described this technique as *neural therapy*. More recently, the effects of “nanogram” dosing of dexamethasone have been reported in the stem cell literature as a means to promote differentiation of mesenchymal stem cells^{32,33}; as a result, some physicians add 30 ng of dexamethasone to the injection solution (Personal Communication, Michael Brown, MD).

Autologous platelet lysate

There are a number of basic regenerative technologies that can be used in some patients with peripheral nerve entrapment neuropathies and nerve injury. Once one gains an understanding of the critical anatomy as well as the ultrasonography skills required to target nerves, there are a variety of injectates available for injection techniques. For example, author M.B. uses an autologous “platelet lysate” (APL) to hydrodissect around a focal entrapment neuropathy or nerve injury. APL is a platelet-rich plasma (PRP) that has had the platelets lysed and the cell membranes and debris removed by filtration. APL has been shown to have natural repair proteomes to support human mesenchymal stem cells^{34,35} and numerous growth factors such as beta transforming growth factor, vascular endothelial growth factor, platelet-derived growth factor, fibroblast growth factor, insulin growth factor (EGF), and epidermal growth factor, which provide a paradigm for healing and repair.³⁴ These platelet-derived factors can stimulate cell replication, promote angiogenesis, and promote tissue granulation formation.

The APL can be made from a patient’s autologous PRP in a number of ways. For example, once the autologous blood has been drawn, spun down, and the PRP separated from the red blood cells and platelet-poor plasma, and aliquot PRP can be injected into a 10 mL sterile red top tube. Calcium chloride or autologous thrombin can be added to the PRP, which activates the platelets and allows a clot to form in the tube, lysing the platelets and releasing the platelet growth factors. An 18-gauge spinal needle with an attached Luer-Lok filter can then be inserted into the tube and a syringe attached to other side of the filter. This provides a means of filtering out cellular debris, leaving plasma (ie, APL) that is rich in platelet growth factors, with increased bioavailability of nitric oxide and reduced levels of 8-Iso-PGF2-alpha, correlating with cell proliferation and migration.^{36,37} This solution can then be injected in a similar fashion to the hydrodissection described earlier, especially for peripheral neuropathies. APL can also be used in the same manner as prolotherapy, for instance, to treat enthesopathies such as lateral epicondylitis.³⁸

The primary advantage of APL over PRP is the lack of white blood cells; some authors³⁹ believe that the white blood cells release proteases and acid hydrolyzes that cause proinflammatory effects.⁴⁰ In addition, wounds with a high level of neutrophils are associated with nonwound healing.⁴¹

Emerging technologies

Revascularization is necessary for tissue regeneration; autologous fibroblasts are a source for therapeutic vasculoneogenesis.⁴²

Another emerging technology for nerve injuries is the use of adipose-derived stem cells (ASC). These cells derived from autologous fat via lipoaspiration have features of multipotential differentiation.⁴³ These cells, which are harvested and digested from the fat stroma and concentrated, have been shown to produce NGF, brain-derived neurotrophic factor, glial-derived neurotrophic factor, and neurotrophin-3 (NT3), which has been detected from cells harvested in both deep and superficial fat layers in the abdomen.^{44,45} Nestin (a neuroectodermal stem cell marker) may help ASC differentiate into neuroglial lineage, and thus ASCs may be used for repair of other structures than just mesodermal lineage.⁴⁶ ASC assays show 3 times more nestin-positive cells in cultures taken from fat than from bone marrow.⁴⁷ Interestingly, cells cultured from lipoaspirates in the more superficial layers of the fat over abdomen were found to be a better source of ASC to use in nerve repair.^{48,49} These cells from the superficial layer significantly enhance neuronal outgrowth in culture compared to cells from the deep layers and did not require stimulation to elicit this response, at least in a study with rat cells. Analysis of neurotrophic factor RNA transcripts showed similar levels of NGF, brain-derived neurotrophic factor, glial derived neurotrophic factor, and NT3 expression in both deep and superficial layer ASC.⁴⁴ Various types of demyelinating peripheral neuropathies (such as complex inflammatory demyelinating peripheral neuropathy) may benefit from ASC.

Complications

Any time you place the needle in the skin, there is a potential chance for infection. This is why sterile skin prep and sterile precautions are used to reduce the risk of these types of complications. There is also the potential of reaction to the medication. Typically, the only medication used that could cause a reaction would be the local anesthetics. Some individuals can be allergic to the preservative in the local anesthetics; the usual preservative, methylparaben, is metabolized to para-aminobenzoic acid, which can be highly allergenic. Reactions can range from a skin rash to full anaphylactic reaction, and it might be wise to routinely use preservative-free medications. Procaine (Novacaine) is often advocated for neural therapy. Although there may be some advantages to using procaine, because it is metabolized into para-aminobenzoic acid, procaine would be expected to cause a higher incidence of allergic reactions than lidocaine.

Any time you are injecting around the nerve, there is a potential for nerve injury, which can be caused by hitting the nerve with the needle, compressing the nerve with too much volume, or injecting inside the nerve bundle. Injecting around the ribs and thoracic cage could potentially cause a pneumothorax. There can also be inflammation associated with the injections, though usually less than that seen by injections of prolotherapy, which is deliberately inflammatory.

Conclusion

The introduction of ultrasound to interventional pain medicine has expanded the modalities available to the clinician and has increased the understanding of the pathology involved in nerve pain. Interventional physicians skilled in ultrasonography are important members of the pain care team of the future, capable of special skills in cell deployment methods that target nerve injury and entrapment neuropathies.

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