Review of ultrasound-guided peripheral nerve stimulation

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INTRODUCTION Peripheral nerve stimulation has been performed for over four decades, but until recently, no minimally invasive technique has existed. A recently described percutaneous ultrasound (US)-guided needle and electrode placement may allow for improvement in patient selection and optimization of the technique.

METHODS The literature on peripheral nerve stimulation and minimally invasive techniques was reviewed using MEDLINE. Anatomical landmarks and potential technical limitations were also reviewed.

RESULTS Review of two anatomical feasibility studies, the original cases series, anatomy texts, and other literature suggest that the potential application of US-guided placement of peripheral nerve stimulation systems is feasible. Application of these techniques will, however, require a significant concentrated experience in US evaluation, cross-sectional anatomy, and nerve block technique before attempting.

CONCLUSIONS There is minimal literature at present to suggest that peripheral nerve stimulation systems should be placed using US or other minimally invasive image-guided techniques. As an emerging technique, significant further research will be required to guide future use.

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Historical perspectives

The Gate Control Theory,1 introduced in 1965, suggested that electrical stimulation might alter processing of noxious afferent nerve transmission in the spinal cord. An important question arising out of Gate Control Theory was whether direct stimulation of nerves could be meaningfully analgesic in humans. Patrick Wall and William Sweet performed seminal experiments using peripheral nerve stimulation (PNS), first to test pain response during stimulation of their own infraorbital nerves, followed by neural stimulation in several patients.2 These first several cases demonstrated that electrical analgesia had significant promise and formed the basis for other neurosurgical techniques. Indeed, one of the earliest patients in the Wall and Sweet series had an electrode placed in the subarachnoid space to evaluate the potential analgesia from that approach. Concurrently, spinal cord stimulation was described by Shealy,3 and this technique became more popular over time.

Various iterations of patch electrodes, circumferential nerve cuff electrodes, as well as the current FDA-approved plate electrode (On-Point; Medtronic, Inc, Min-
neapolis, MN) were developed and implanted in several larger case series for the treatment of peripheral nerve pain syndromes. Complications of peripheral nerve stimulation procedures were recognized early, as lead migration, neuropraxia due to nerve irritation, loss of stimulation, and other equipment-related technical problems dampened some of the early enthusiasm. Lower extremity targets seemed to have poorer outcomes compared with upper extremity PNS. To reduce neural irritation, many authors recommended an intermediate fascial graft be placed between the nerve and electrode, either harvested locally or from a remote site, as concerns over stripping the perineural fascia and surrounding tissue were described. Surgeons were appropriately concerned that local anatomical factors, the small vascular supply to the nerves (vasa nervorum), other arterial vessels, nerve branches, and potential anatomical variations needed to be accounted for in these procedures. Even in early experiments, it became apparent that the intraneuronal fascicular arrangement was important to both the functional outcome and the therapeutic window of stimulation. Sunderland described the arrangement of these intraneuronal fascicles in upper extremity nerves relative to the nerve cross section at various points along the nerve and found that the orientation was quite variable. In fact, position of any given fascicle might change 180 degrees within a span of less than 2 cm. The intraneuronal fascicular arrangement is important when stimulating a peripheral nerve; for example, the fascicle devoted to the superficial radial nerve sensory branch may be either medial, lateral, deep, or superficial depending on the exact site of stimulation (axillary, midhumeral, or supracondylar) and the particular anatomical arrangement in that patient (see Anatomical Considerations section). Nashold and coworkers advocated for intraoperative stimulation to optimize close approximation of the stimulated electrode near the desired fascicle (Figure 1). In the same manner, placing electrode arrays too close to motor fascicles may result in excessive motor stimulation, which can be either irritating or even painful. The idea of stimulating a motor fascicle at the expense of the desired sensory fascicle is manifested clinically as a very narrow therapeutic window for peripheral nerve stimulation therapy. Thus, a patient may have excellent analgesia with initial amplitude, but with a very slight increase in voltage, alteration of the pulse width, or a change in frequency, the patient might have unacceptable motor activation in the involved extremity. Migration of leads can also become problematic, wherein a previously helpful stimulation program can either lose efficacy or even become bothersome due to movement of the cathode closer to an undesired motor fascicle. As with spinal cord stimulation, migration can be a frustrating problem for clinicians and patients alike. One series of peripheral nerve stimulator implants at a large tertiary center resulted in the need for 1.6 revisions per patient, on average, not counting battery replacements. These authors performed permanent implants from the outset, without a temporary trial extension, reasoning that the vast majority of patients would be permanently implanted anyway. Thus, the lack of a minimally invasive trial led to a small but significant percentage (approximately 5% to 10%) of patients who had trial systems placed that were not analgesic and required explantation. In modern neurosurgical practice, implantation of a peripheral nerve stimulation system requires open surgical dissection. Patients with failed systems who desire explantation must undergo a similarly invasive procedure to remove the device.

**Early development of minimally invasive PNS techniques**

Percutaneous techniques for the treatment of peripheral nerve pain date back to 1978 and the introduction of percutaneous trigeminal nerve stimulation via a needle advanced through the foramen ovale. In recent years there has been a surge in placement of supraorbital nerve and occipital nerve stimulation electrodes using fluoroscopic guidance or without image guidance. These techniques are essentially a variation of peripheral field stimulation, as the nerves or other soft tissue structures (vessels, muscles) are not visualized, and the electrode is implanted based on expected nerve location relative to visualized bony landmarks.

Two recent feasibility studies examined the potential for using ultrasound (US) for image-guided placement of electrodes. It was hypothesized that, similar to US-guided nerve block procedures, one might use US to directly visualize the nerves and their surrounding fascia, blood vessels, muscles, and other tissues in real-time. The operator would...
then be able to place the stimulation contacts very close to the target nerve. The studies of cadaver lower and upper extremity specimens convened to further elaborate potential good imaging locations and potential pitfalls of the technique compared with open surgical placement.

**Anatomical considerations**

In normal human anatomy, peripheral nerves contain various connective tissue sheaths, including the epineurium, perineurium, and endoneurium (Figure 2). The tissue that surrounds the nerve (epineurium) is very tough, protecting the internal neural contents. The perineurium, consisting of squamous epithelium and connective tissue, divides the intraneural fascicles and branches concurrently with each of the fascicles at branch points in a tubular fashion. Internal to each fascicle is a delicate layer of endoneurium that surrounds individual nerve fibers. Branch points are not merely a separation of axons, but that of individual fibers. The intermingling of these various fibers produces abundant variability. Peripheral nerves of the extremities must be able to freely move, gliding within muscular layers with surrounding fascia. Often, a nerve may move several millimeters, and neighboring structures, such as electrodes that have rough irregular surfaces could produce friction as the nerve slides by. Normal nerve motion is thus critically important to any implant procedure for nerve stimulation. Open surgical placement of peripheral nerve stimulation electrodes has been performed at several key sites. The rationale for choosing particular target sites for peripheral nerve stimulation includes: (1) anatomical ease of nerve localization; (2) local anatomical features (arterial structures, including the vasa nervorum, available fascia for interposed graft, number/location of nerve branch points, need for traversing muscular planes); (3) potential neural fascicular arrangement at the site; and (4) potential nearby sites for pulse generator implantation and ease of extension tunneling. Many of these same concepts are applicable to placement of peripheral nerve stimulation hardware using US-guidance. Anatomical considerations for peripheral nerve stimulation substantially differ from those for spinal cord stimulation in several ways. Whereas the location of the dorsal columns and zone of appropriate paresthesia are somewhat predictable for spinal cord stimulation, the course of peripheral nerves and target sensory fibers within those nerves are less predictable. For example, when one chooses a location for targeting a particular nerve with US, the following features are helpful: (1) the nerve should be a minimal distance from the surface to allow for better acoustic contrast and resultant visual clarity; (2) the nerve should be approached in areas where surrounding adipose/connective tissue is prevalent, as this helps with visualization and buffers the nerve from compression or scar impingement; (3) minimizing lead passage through abundant muscle tissue will decrease local bleeding and limit the effects of muscle contraction on lead retraction and migration; and (4) pre-scanning for presence of anatomical variations, such as a Martin-Gruber or other nerve anastomoses, collateral arteries that may potentially be injured, or other vulnerable anatomical features. Previous feasibility studies in cadavers outlined some of these potential sites and will be described relative to several target nerves.

**Radial nerve**

The radial nerve was approached in cadaver studies at a point approximately 10-14 cm above the condylar line. This site is proximal to most of the sites of radial nerve painful syndromes, such as lateral epicondylitis, entrapment neuropathy, extensor tenosynovitis, etc. The radial nerve splits inferior to the condylar line into deep and superficial radial branches. Subsequent placements in patients have been at similar locations as described in anatomical studies, as well as targeting the superficial radial sensory branch in the forearm. In the area inferior to the spiral groove, but superior to the condylar line, the radial nerve is relatively close to the surface, near the lateral head of the triceps muscle and in close approximation to the humerus. The nerve is scaphoid in appearance and well visualized with a high-frequency transducer (Figure 3). Attention should be placed on the location of the profunda brachii artery and vein, which run with the radial nerve in the midhumeral area. The profunda brachii supplies a nutrient branch to the humerus, as well as muscular branches. In addition, the radial collateral artery and the middle collateral branch of the profunda brachii artery may be encountered. Generally, only the profunda brachii or the radial collateral artery or muscular branches are seen in the area of scanning herein described. The radial collateral artery is the continuing branch of the profunda brachii; it passes between the brachialis and brachioradialis to supply the radial nerve, the muscles above, and smaller perforators. It may join with the ascending radial recurrent artery near the elbow.
Ulnar nerve

The ulnar nerve was approached on the medial upper arm, also at approximately 10-14 cm above the condylar line. Here, the nerve lies medial to the medial head of the triceps. Many patients have had prior surgical treatment for neuropathic pain, including nerve transposition surgery as treatment for a cubital tunnel entrapment syndrome. In cases of previous surgery, the entry point for the needle and subsequent electrode is often just proximal to the existing scar. The humeral bone will have a hypoechoic appearance on US with a hyperechoic edge. The needle and electrode were generally placed lateral or deep to the nerve with the electrode passing under the nerve in an oblique or transverse orientation (see Figure 5). Care must be taken to avoid the superior ulnar collateral artery and the medial brachial cutaneous nerve. The superior ulnar collateral artery runs with the ulnar nerve, pierces the medial intermuscular septum, and supplies the medial head of triceps. Minimal disruption of other anatomical structures, particularly nerve nutrient vessels, is paramount to success, or the advantages of minimally invasive technique quickly dissipate.

Median nerve

The median nerve is easily accessible at locations above or below the elbow. Approximately 6 cm superior to the condylar line, the nerve is immediately medial to the brachial artery. Distal to the condylar line as the nerve leaves the cubital fossa, it passes anterior to the brachialis muscle and medial to the brachial artery, passes between the two heads of pronator teres (occasionally posterior to both), and gives off muscular branches. Due to the minimal number of branches above the elbow, the nerve may be targeted better there.

Sciatic nerve

The sciatic nerve is generally targeted at the superior aspect of the popliteal fossa immediately before its bifurcation. Either the common peroneal or tibial nerve branch (or both) may also be targeted at this location (Figure 4). The human fascicular arrangement is less well characterized at this location than the elegant work of Sunderland in the upper extremity. The US imaging appearance of the sciatic nerve between the ischium and greater trochanter had previously been described by Chan and coworkers. In human volunteers, using a low-frequency probe, the sciatic nerve can usually be visualized as a ellipsoidal structure in the ischial–trochanteric groove deep to the gluteus maximus musculature. In a recent case of a patient with prior sciatic dissection for tumor, the nerve could be visualized well. An implanted trial electrode anterior to the nerve provided 100% short-term relief before removal.

Tibial nerve

The tibial nerve may be either targeted immediately past the bifurcation of the sciatic nerve or in an area superior to the tarsal tunnel. The popliteal area is ideal for US placement as the nerve is close to the skin surface and surrounded by adipose and favorable acoustic features. The area approximately 10-14 cm superior to the tarsal tunnel was also noted to be a reasonable approach with US in previous cadaver work. The tibial nerve approach above the ankle requires one to place the needle very close to the tibial bone and navigate the local muscular tendons (flexor hallucis longus, tibialis posterior, and flexor digitorum longus).

Peroneal nerve

The common peroneal can be easily seen with US at the fibular head, but the minimal skin to nerve distance and fibular bone proximity makes placing a long electrode problematic at this location using US guidance. Thus, the peroneal nerve may be more easily targeted at the upper popliteal area, as described for the tibial nerve. Distal applications to selectively target the superficial peroneal nerve may be possible.

Programming

In our previously reported series of US-guided placement, we used a variety of programming schemes. Intensity settings for patients receiving Boston Scientific systems ranged
from 1.4 to 10.4 milliamps. For patients receiving Medtronic systems, intensity was 0.7-3.6 V. Interestingly, in almost all cases, we were able to find a stimulation intensity that was below perceptible levels for paresthesia, but still produced analgesia. Pulse width ranged from 130 to 490 microseconds, with no clear association to nerve stimulated. Frequency ranged from 40 to 90 Hz. Use of a small number of contacts was found to produce maximum analgesia with minimum motor stimulation and unpleasant paresthesiae. Generally, no more than two anodes were used, consistent with our observation that target peripheral nerves treated in our series spanned no greater than the opposite ends of two adjacent contacts (both for the eight-contact electrode from Boston Scientific, Valencia, CA, and the 8-contact Sub Compact electrode from Medtronic, Minneapolis, MN) (Figure 5).

**Mechanism of action**

The precise analgesic mechanism of action of peripheral nerve stimulation for peripheral neuropathic pain is not fully
elucidated. The most likely mechanisms include (1) gate control within the spinal cord or at supraspinal locations; (2) antidromic interruption of afferent nociceptive impulses from the periphery; (3) inhibition of spontaneous activity of neuromas; (4) prolonged alteration of processing through modulation of neuroplasticity within the dorsal horn, spinthalamic tracts, or at supraspinal locations; and (5) alterations in vascular and nonvascular smooth muscle tone associated with neurohumoral modulation. In vivo and in vitro experiments suggest each of these potential mechanisms, with perhaps neurona inhibition and gate control having the most credible evidentiary support in animal models.

A single study in human volunteers reported laser intensity pain ratings and cortical laser-evoked potentials during and shortly after experimental percutaneous electrical stimulation of the radial nerve. Subjects noted a reduction in pain ratings during stimulation (“stim-on”) but not in the period immediately after (“stim-off”). However, cortical potentials were altered both during and after stimulation, even when peripheral nerve stimulation was administered contralateral to the site of laser stimulation, suggesting immediate and prolonged alteration of supraspinal pain processing. Although the mechanisms suggested are compelling, it should be noted that the authors used a nociceptive (rather than neuropathic) model, reducing the generalizability of their results to patients receiving peripheral nerve stimulation systems, who most commonly have primarily neuropathic pain. In addition, peripheral nerve stimulation may share some mechanisms with spinal cord stimulation. Based on animal models, electrical stimulation of the dorsal columns may be analgesic in different ways, partly dependent on the specific disease state. Reduced hyperexcitability of wide-dynamic range neurons and increased levels of γ-aminobutyric acid (GABA) are seen with spinal cord stimulation for neuropathic pain. In patients with ischemic pain, analgesia is thought to occur either through redistribution of blood flow or reduction of tissue oxygen demand.

As alluded to above, in an animal model, peripheral nerve stimulation induced changes in smooth muscle tone, probably via modulation of nitric oxide (NO) levels. Because the changes in blood flow that follow spinal cord stimulation may also rely on NO (in addition to calcitonin gene-related peptide), the potential for mechanistic overlap exists. The modulation of vasomotor activity seen with both peripheral nerve and spinal cord stimulation may also help to explain the beneficial effects of neurostimulation for complex regional pain syndrome.

Research and technology

Peripheral nerve stimulation, although a promising therapy, has low quality evidence to support it. Thus, there is tremendous need for improvement in the available electrode and battery designs to support minimally invasive therapies, such as those described herein. A means of performing a minimally invasive trial has been sorely lacking for PNS therapy. Thus, US-guided strategies for targeting peripheral nerves may reduce morbidity and increase acceptability of this therapy. A promising alternative and emerging technology to the use of electrodes designed for epidural use is the bion, a small, electrode-generator system that can be implanted in close proximity to target peripheral nerves and obviates the need for tunneling to a remote generator site. Whereas the authors of the first paper documenting its use in humans used a stimulating needle to locate the target nerve (the occipital nerve for purposes of the study), US could be used as an alternative technique.

Future advances in technology for peripheral nerve stimulation might include (1) alternative electrode designs that can be implanted using a minimally invasive technique and allow precise targeting of sensory fascicles, or (2) improved pulse generators that are very small but do not require frequent charging. Along with technological advances, stronger evidence is needed. Future studies should employ a randomized, sham-controlled design. Minimally invasive techniques should improve the acceptability of sham implantation, allowing for the collection of evidence of the highest standard possible.

References


