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A Resurgence of Peripheral Nerve Stimulation with Innovation in Device Technologies

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Within the last decade, implantation of peripheral nerve stimulation (PNS) devices has evolved from an open neurosurgical technique to primarily an outpatient procedure. The initial application of PNS involved off-label modification of traditional spinal cord stimulation (SCS) systems.¹ However, many of the design properties advantageous for SCS were not optimal for PNS. Semi-rigid electrodes were often tunneled long distances from the implantable pulse generator (IPG) and sutured in a cuff-like manner to the target nerve under direct visualization.¹ These modified systems were prone to migration, infection, lead fracture, erosion, and generator site discomfort.² Recent innovations in PNS technology have miniaturized and sometimes externalized IPGs, with electrodes specifically purposed for PNS.³

The simplified implantation techniques have drawn interest from physicians across multiple specialties who had not previously exploited the surgical placement of SCS leads on a peripheral nerve. Furthermore, pairing PNS systems with ultrasound guidance has unlocked the potential for varying waveform effects on a peripheral nerve.^{4, 5} Along with increased accessibility of ultrasound, this generation of PNS systems may revolutionize pain control around the world. The expanding applications, number of implanters, technological innovation, and pressing need for opioid-alternatives have brought PNS to the forefront of promising new pain treatment modalities.⁶

One area of expanding application falls within the domain of perioperative pain management. In this issue of *Regional Anesthesia and Pain Medicine*, Gilmore et al.⁷ examine the use of PNS for the treatment of chronic neuropathic pain in amputees. The PNS device studied is approved by the Food and Drug Administration (FDA) for up to 60 days of application in the back and/or extremities for the following indications: 1) Symptomatic

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relief of chronic, intractable pain or post-surgical and post-traumatic acute pain; 2) Symptomatic relief of post-traumatic pain; and 3) Symptomatic relief of postoperative pain.⁸ This article is the latest in a series of investigations examining the efficacy of a dedicated PNS system (SPRINT®, SPR Therapeutics, Cleveland, OH).^{9–12} These studies were primarily feasibility-based case series that demonstrated potential utility for post-amputation pain, postoperative pain after total knee arthroplasty, chronic low back pain, and, most recently, postoperative pain after rotator cuff repair.^{9–12} The foundation for the present work was put forth by Rauck et al.,⁹ who targeted the sciatic and femoral nerves in patients with chronic neuropathic pain categorized as residual limb pain and/or phantom limb pain.

Gilmore et al.⁷ present a multicenter, randomized, double-blinded, placebo-controlled, partial-crossover study that was carried out in an amputee population (n=28). All patients were implanted with PNS leads and were administered either active stimulation or placebo sham stimulation for the initial 4 weeks, with crossover of the placebo group after 4 weeks (weeks 5–8). In question may be the use of sham stimulation (which can be described as paresthesia-free) even though blinding may be achieved with appropriate research design. Nevertheless, the minimally invasive nature of modern PNS implantation may for the first time allow true placebo groups

Although their primary outcome of >50% pain relief at 4 weeks was met in the treatment arm, surprisingly, the crossover patients did not have similar results.⁷ All leads were placed under ultrasound guidance, but stimulation testing was not performed for patients in the “placebo arm.” The results may justify lead testing in future studies to ensure optimal placement of the PNS lead. Additionally, early intervention with PNS after surgical injury may provide better outcomes than delayed application. Furthermore, it has been suggested that PNS may be more effective for phantom limb pain than for residual limb pain (weeks 1–8). This idea challenges the older dogma that phantom limb pain is a centrally mediated phenomenon that is best treated with centrally targeted therapies (i.e., dorsal column stimulation, mirror box therapy).^{13–15}

Strikingly, some patients obtained long-term benefit from the 8-week PNS treatment. The mechanism(s) by which PNS provides a lasting treatment effect are unclear but may be related to neuronal plasticity and reorganization both centrally and peripherally.^{16; 17} As synaptic plasticity surrounding the time of injury may promote the development of chronic pain, earlier and/or pre-emptive intervention with PNS may provide additional benefit.^{16; 18} Moreover, animal work by Sun et al.¹⁹ suggested that receptor levels may change in the spinal cord secondary to peripheral nerve stimulation. Understanding the electrical effects on a peripheral nerve is paramount to optimizing the use of PNS systems.

As a group, PNS implanters should be sensitive to costs and safety concerns for the perioperative patient because not all patients will develop refractory chronic pain and most will improve regardless of intervention. Though this study examined PNS in patients multiple years from the time of injury and amputation, the safety profile is relevant for perioperative patients. This study is noteworthy for a 15% lead fracture rate; however, infection risk was minimal.^{7; 20} This may be compared to complications in other emerging

stimulation modalities such as dorsal root ganglion stimulation.²¹ Nonetheless, PNS use in the perioperative phase should underscore the reduction of opioids in this population.

This study appears to be the structure for a larger randomized controlled trial already underway for the same indication, but with a parallel-group design (NCT03783689). As this study was funded by the Department of Defense, another valuable benefit to noninvasive PNS techniques may be their applicability to deployed settings far from the resources of a tertiary facility. Similarly, the military is also leading the way with the Defense Advanced Research Projects Electrical Prescriptions (ElectRx) program, which is investigating neuromodulation of peripheral nerve targets for pain, general inflammation, post-traumatic stress, severe anxiety, and trauma.²²

The article by Gilmore et al.⁷ in this issue emphasizes the renaissance of PNS in the 21st century. Beyond its application for pain treatment, electrical stimulation of peripheral nerves has demonstrated potential in neural regeneration.²³ For example, electrical stimulation of the median nerve after carpal tunnel release resulted in reinnervation of the thenar muscles within 6 months.²⁴ Also, implantable PNS systems that stimulate the tibial nerve in patients with overactive bladder could eliminate the repeat visits necessary with percutaneous stimulation techniques.²⁵ Moreover, median nerve stimulation is an interesting application for the treatment of arrhythmias.^{26; 27} An animal model of electroacupuncture in cats has shown that median nerve stimulation may diminish myocardial ischemia through a sympathetically mediated mechanism.²⁸

While new applications are explored, established PNS indications may be optimized through modification of waveform parameters, precise placement of stimulation leads, and electrical dose delivery to the target nerve. Concepts of duty cycle and electrical dosing under investigation with SCS may also relate to PNS.²⁹ The multitude of waveforms available for SCS and transcutaneous electrical nerve stimulation should provide a framework for future research in waveform theory. We commend work in the field of PNS as the stage is set to revolutionize regional anesthesia and pain medicine in the 21st century.

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