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PERIPHERAL LOW FREQUENCY VERSUS HIGH FREQUENCY NERVE STIMULATION: A CASE SERIES

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Background: Peripheral nerve stimulation is a therapeutic option for managing chronic neuropathic pain. After a thorough clinical evaluation—including a medical history review and, when appropriate, diagnostic anesthetic injections—a specific nerve associated with the pain can be identified. A peripheral nerve stimulator may then be implanted near this target nerve. The device delivers controlled electrical impulses that disrupt pain signals, offering varying levels of relief.

Case Report: This case series compares the clinical efficacy of low frequency vs high frequency peripheral nerve stimulation therapy in 2 patients with Complex Regional Pain Syndrome Type II. Both patients had experienced inadequate pain relief from low frequency therapy devices and were subsequently treated with receiver based peripheral nerve stimulators capable of delivering higher frequencies; both patients then had clinically significant pain improvement.

Conclusion: These cases show the potential for high frequency—compared to lower frequencies—peripheral nerve stimulation for treating pain more effectively in selected patients with neuropathic pain..

Key words: Chronic pain, peripheral nerve stimulation, case series, Complex Regional Pain Syndrome, CRPS

BACKGROUND

Peripheral nerve stimulation (PNS) is a treatment for managing chronic neuropathic pain. Once a diagnosis of chronic neuropathic pain is established through clinical evaluation, medical history, and, if necessary, diagnostic anesthetic injections, a peripheral nerve stimulator may be placed near the nerve identified as the pain source. The electrical impulses delivered by the system interfere with pain perception, providing varying degrees of pain relief (1-4).

The neurostimulators evaluated in our patients were powered using 2 different approaches. The first employed a nonrechargeable implantable pulse generator (IPG). The 2 patients in our study received the LIGHTLINE 150 IPG (NEURIMPULSE s.r.l.) (Editor's note: this device is not approved by the US Food and Drug Administration). The second approach involved powering the implanted receiver based neurostimulator through wireless energy transfer; for these cases, we used the Freedom® PNS System (Curonix LLC). The transmitter is rechargeable. The power source is not the only difference between the 2 systems. The stimulator with a nonrechargeable IPG can only deliver frequencies up to 100 Hz, which is perceived as a tactile sensation or tingling, called paresthesia, whereas the receiver based system can reach 1,499 Hz. This difference results in a different sensory experience for the patient; stimulation at 1,000–1,499 Hz falls within the

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"paresthesia-free" range, meaning it is not perceived by the patient ("subthreshold").

This case series presents 2 patients who, due to the ineffectiveness of low frequency therapy stimulation, had the original devices explanted and replaced with high frequency therapy devices.

METHODS

Device Description

The receiver based peripheral nerve stimulator system used in our 2 patients includes an implanted electrode array (with 4 or 8 contacts), a separate implanted receiver, as well as a transmitter assembly and wearable accessory (Fig. 1). The transmitter uses high frequency electromagnetic coupling (HF-EMC) technology to wirelessly transfer data and radiofrequency energy to the 2-component implant that the physician connects during the procedure. The physician must also create a separate, distinct pocket to permanently anchor the device.

Permanent Implant Surgical Technique

Written Informed consent was obtained from both patients. They were taken to the operating room and appropriately positioned on the table. The implant site was surgically prepped and covered with sterile drapes. The needle entry and trajectory were planned using palpation and either fluoroscopy or ultrasound. The skin and deeper tissues were anesthetized using a local anesthetic. The initial introducer path was also infiltrated with a local anesthetic. The first incision was made with a #11 blade scalpel, then a 13G introducer cannula was passed through the incision and under imaging guidance advanced subcutaneously in the fascial plane to the target nerve. A 4-contact electrode array with tines was inserted through the cannula and advanced to the target nerve.

A second distinct incision was made using blunt dissection to create a receiver pocket. The steering stylet was removed from the previously implanted electrode array. A separate receiver was connected to the electrode array. After being connected, the electrode array and receiver were tunneled to the receiver pocket. The receiver was coiled and secured with 2 nonabsorbable sutures. The receiver coil's end was tucked underneath the coil to avoid soft tissue erosion. Using a nonabsorbable suture, the receiver coil was sutured to the fascia in at least 2 locations, ensuring that the coil was flat in the pocket. The receiver pocket was closed with deep and superficial absorbable sutures.

Programming Protocol

The devices were programmed with a subthreshold protocol using a frequency of 1,499 Hz with a pulse width of 30 μs at variable intensities (mA). The transmitter and antenna were in an external wearable.

CASE PRESENTATIONS

Case One

An 83-year-old woman presented with Persistent Spinal Pain Syndrome (PSPS) Type II. In 2015, she underwent a trial and subsequent implantation of a spinal cord stimulator which was only partially effective in the long-term and was explanted in 2018. That same year,

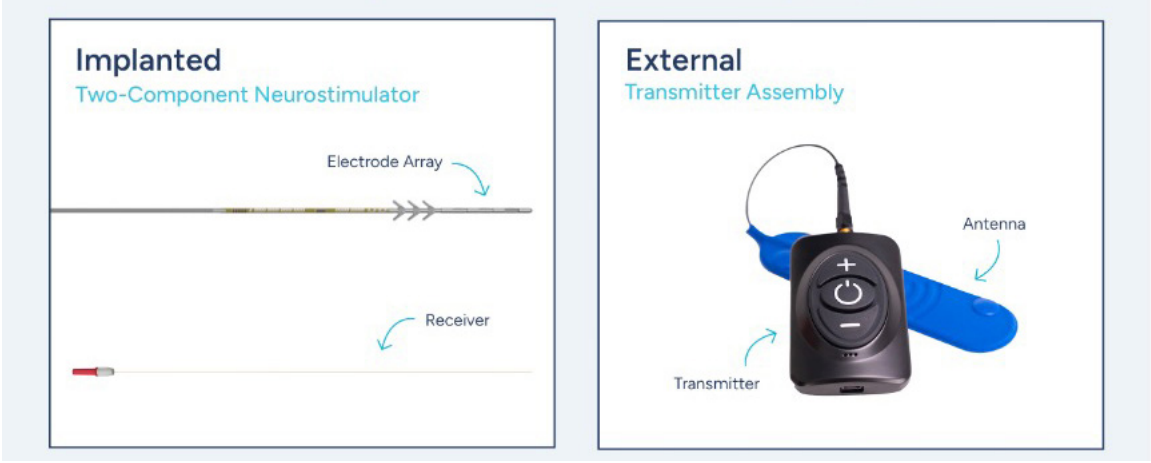

Fig. 1. Freedom PNS System.

an intrathecal drug delivery pump was implanted. It provided partial pain relief for her lumbar pain.

In 2020, during hospitalization for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pneumonia, she developed a large hematoma in her right arm following an arterial puncture. This led to Compartment Syndrome, requiring fasciotomy. Healing was incomplete; an eschar formed and the hematoma reoccurred, which was managed conservatively. She subsequently developed neuropathic pain, likely due to an injury to the right median nerve. Initially, a perineural catheter was placed at the brachial plexus for a few weeks with anesthetic infusion to manage pain. In 2022, at another health care facility, she received a peripheral nerve stimulator (LIGHTLINE 150 [NEURIMPULSE s.r.l.]) with a nonrechargeable IPG that targeted the brachial plexus with an infraclavicular approach.

She was initially stimulated at 50 Hz and tried multiple stimulation intensities. Despite achieving good paresthesia coverage, she had no pain relief. She then underwent the implantation of a 32-contact spinal cord stimulator at another medical center, aiming to cover both her arm and back/leg pain. The cervical electrode was placed with its tip at C3, while the 2 lumbar electrodes were positioned between the inferior margin of T8 and T11. However, since she had no pain benefit, it was removed in 2023.

The patient continued to be monitored and received intrathecal pump refills at our center. In May 2024, due to the lack of pain relief from the peripheral nerve stimulator, she requested its removal. At that visit, she presented with a swollen right hand and significant functional impairment. The Budapest Criteria for a Complex Regional Pain Syndrome diagnosis were met, specifically: severe burning pain (Numeric Rating Scale [NRS-11] of 9), right hand edema, allodynia, and functional impairment. Her DN4 score was 5, although hypoesthesia to touch and pinprick could not be assessed due to extreme pain upon contact.

A cervical ganglion stimulator was proposed, but the patient declined. Instead, she agreed to try replacement with an externally powered neurostimulator (Freedom® PNS System). In March 2024, under ultrasound guidance, it was implanted in the right infraclavicular periplexus region, with the antenna positioned along the ipsilateral humerus (Fig. 2). The device was programmed with stimulation at one kHz, and 30 µs pulse width. She uses the system for a total of approximately 18 hours per day.

At her 6-month follow-up, her NRS-11 score was 3, there was improved skin trophism, a significant reduction in edema, a resolution of allodynia (which had previously prevented hand function), and a DN4 score of one. At the one-year follow-up, the results remained stable, with no device malfunctions. No device-related adverse events were reported.

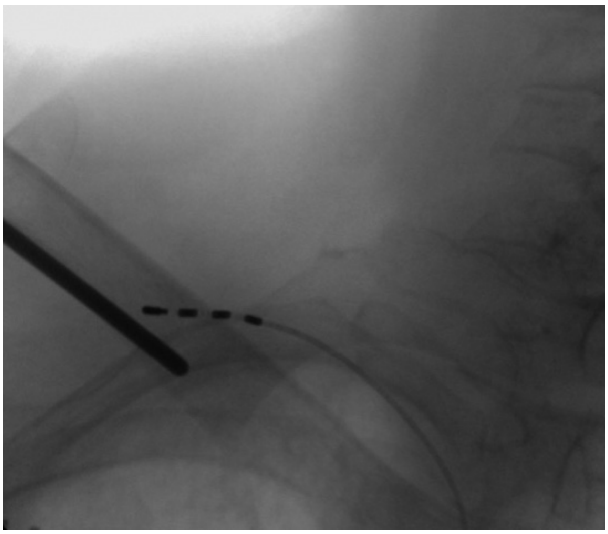

Fig. 2. Case one x-ray.

Case 2

A 75-year-old man underwent arthroscopic right carpal tunnel surgery in 1996. The surgery resulted in an iatrogenic lesion of the right median nerve. Subsequently, 2 neurolysis procedures were performed in an attempt to control his intense pain symptoms, but the procedures were not a success. In 2007, he was treated with a sural nerve graft, also without positive results. Two sessions of pulsed radiofrequency on the median nerve were conducted in 2013; they produced no significant improvement.

On physical examination he had right hand allodynia, hyperalgesia, paresthesia, dysesthesia, burning pain, and altered thermoregulation and thermotactile sensation. All of these symptoms were compatible with CRPS Type II, according to the Budapest Criteria. His pain radiated along the arm toward the shoulder and was not limited to the area of the median nerve. He also had ankylosis of the distal phalanges and reported dystonic episodes in the hand. An electromyography test did not reveal sensory and motor potentials in the right median nerve.

In 2013, after the 2 PRF sessions, he underwent implantation of a peripheral nerve stimulator with a

nonrechargeable IPG on the electrodes on the ulnar and median nerves, which initially improved his pain; his NRS-11 score went from 9 to 6. No other measurements were recorded.

In November 2024, the peripheral nerve stimulator electrodes and battery were removed due to its diminished efficacy and battery depletion. At the same time, a percutaneous implantation of a receiver based peripheral neurostimulator (Freedom PNS System) was performed at the level of the median nerve in the forearm (Fig. 3). Before this procedure, he was treated with tapentadol 150 mg twice a day; cannabis flos 6% tetrahydrocannabinol (THC) and 7.5% cannabidiol (CBD); amitriptyline 12 mg twice a day; and gabapentin 400 mg 3 times a day. His preoperative NRS-11 score was 10 and his EuroQol 5-Dimensions 5-Levels (EQ-5D-5L [EuroQol Research Foundation]) score was 14,555 (quality index -0.201). The device was programmed with stimulation at 1,499 Hz, and 30 μs pulse width.

His postoperative NRS-11 score was one, and at his one month follow-up, his EQ-5D-5L score was 12,122 (quality index 0.863). After 3 months, his EQ-5D-5L score remained at 12,122 (quality index 0.863), his NRS-11 score remained at one, and his persistent painful paresthesia of the first, second, and third fingers disappeared.

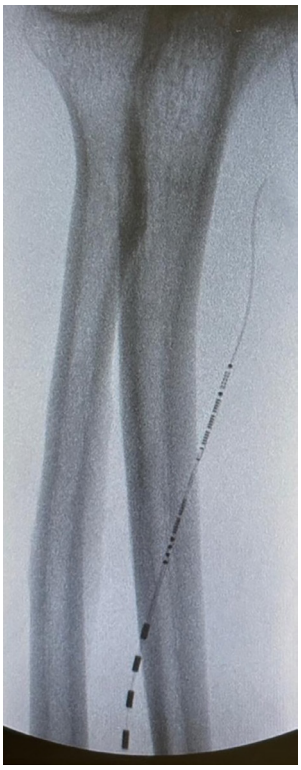

Fig. 3. Case 2 x-ray.

Amitriptyline was then discontinued. No device-related adverse events were reported.

DISCUSSION

PNS is a valid alternative to more proximal neurostimulation when pain is limited to one or 2 nerve territories. PNS offers the advantage of a smaller device and better energy targeting to the painful area, thereby saving battery life and avoiding unnecessary stimulation of unaffected regions (5).

The 2 patients in this case series presented with CRPS Type II for whom dorsal root ganglion (DRG) stimulation could be considered the first choice. Although C6 DRG stimulation is technically possible, for compatibility the battery has to be placed in the upper abdomen, which was not feasible here. Batteries are typically placed in the gluteal area, but this would require an extension, compromising magnetic resonance imaging conditionality. The LIGHTLINE 150 is not currently MR conditional , whereas the Freedom PNS System is MR conditional at 1.5T in Europe and 1.5T and 3.0T (available only for the 4-contact electrode array) in the United States.

In these cases, the first patient refused DRG stimulation, due to her fear of removing the previous spinal cord stimulator implant, while the second patient was never offered DRG stimulation as an option. These 2 cases highlight an important clinical issue: in both patients, low frequency stimulation provided valid paresthesia coverage over the painful area, without discomfort, but also without pain relief. Replacing the low frequency device with a receiver based PNS with high frequency capabilities led to better pain control without any stimulation discomfort.

The mechanism of action behind low frequency (tonic) peripheral neurostimulation is still based on the Gate Control Theory by Melzack and Wall (6), where the activation of large-diameter sensory fibers inhibits nociceptive transmission in the dorsal horn. This results in paresthesia over the painful area. However, in both patients in this case series, although paresthesias were well-targeted, they did not translate into pain relief.

The mechanism of action of high frequency peripheral stimulation is not completely understood. On the motor side, it has been shown that "superactivation" of a peripheral nerve can be achieved with less energy if stimulation is delivered at a higher frequency (7), suggesting that stimulation frequency plays a key role. There are also some studies on sensory nerve conduction

block using high frequency stimulation, particularly kilohertz frequency alternating current (8,9). The Freedom PNS System uses stimulation patterns with frequencies at a maximum of 1,499 Hz. This kind of stimulation seems able to modulate or block sensory conduction (10). One study suggested that pulse trains that exceed 150 Hz can influence axonal activity by interrupting evoked excitation, thereby leading to a partial or complete block of conduction, depending on frequency, rather than amplitude (11).

Based on these observations, it is clear that high frequency and low frequency PNS are fundamentally different therapies. Low frequency stimulation acts peripherally to generate signals that centrally override pain, whereas high frequency stimulation acts peripherally by directly modulating or blocking pain transmission. This could explain the different responses in these 2 patients.

In addition to the known mechanism of action of PNS on the periphery as explained by The Gate Control Theory, there is evidence that PNS also has a central mechanism of action. PNS modulates central nervous system centers, including the dorsolateral prefrontal cortex, somatosensory cortex, anterior cingulate cortex, and parahippocampal areas. It has also been proposed that PNS can exert an effect on GABAergic and glycinergic transmission at the spinal level, inhibiting the dorsal wide dynamic range neurons, reducing Aδ fiber activation, and affecting the spinothalamic tract (12).

Clinical use of PNS in the past was limited by the invasiveness of the procedure and complications like lead migration or fracture. With current miniaturized and receiver based systems, PNS is a less invasive and much more feasible option.

Limitations

These observations are based on a limited 2-patient case study; therefore, clinical outcomes may vary among patients.

CONCLUSION

This case series reports the direct comparison between low-frequency and high-frequency PNS in the same patients. Receiver based high-frequency stimulation provided improved pain control and was well tolerated, suggesting that stimulation frequency may play a crucial role in the effectiveness of PNS.

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