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Peripheral Nerve Stimulation: From Nerve Blocks to Wireless Neuromodulation

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Abstract

Peripheral nerve stimulation (PNS) was one of the earliest neuromodulation modalities to be applied clinically soon after the Gateway theory. Prior to PNS, anesthetic nerve blocks were used for pain relief and surgical procedures. From nerve blocks to stimulation, PNS has evolved rapidly in techniques and technology leading to the minimally invasive wireless neuromodulation. Peripheral nerve blocks were applied clinically to predict PNS outcomes. Not only these studies revealed the prognostication of neuromodulation but led to observations to modify PNS also. Accordingly, nerve stimulation along the major nerve or along its branch or the nerve field yielded similar outcomes in experimental as well as clinical settings. This also facilitated approaches with minimalistic surgical procedure, single step implantations without trial stimulation. Wireless PNS enhances the outcomes due to its inherent advantages like minimal tissue trauma, absence of implantable pulse generator (IPG) or the accessories required for traditional PNS. Preliminary case illustrations demonstrated the safety of this wireless technology and further long-term outcome studies in larger patient populations are in progress.

Keywords: Peripheral nerve stimulation; Nerve blocks; Wireless; Neuromodulation

Abbreviations: PNS: Peripheral Nerve Stimulation; IPG: Implantable Pulse Generator; RCT: Randomized Controlled Trial; PENS: Percutaneous Electrical Nerve Stimulation; TENS: Transcutaneous Electrical Nerve Stimulation; PSFS: Peripheral Subcutaneous Field Stimulation; EA: Electro Acupuncture; SQS: Subcutaneous Nerve Stimulation; RF: Radiofrequency; CTNS: Chronic Tibial Nerve Stimulator; DC: Direct Current; 4-AP: 4-amino-pyridine; GHz:Giga Hertz; WPG: Wireless Power Generator.

Introduction

Ronald Melzak and Patrick Wall in 1965, introduced the theory of pain [1], while William Sweet and Wall provided the proof of concept for PNS in 1967, when they stimulated their own infraorbital nerve using a needle electrode; thus, reporting the results of electrical stimulation for the first time, with first- hand experience [2]. Subsequently, PNS was enthusiastically used for chronic pain relief but with mixed results, predominantly due to poor selection criteria, technical difficulties and failure of systematic application [3]. As a result, there has been very limited authentic literature on PNS validating its efficacy, although the beginnings were exciting [4]. However, PNS has the potential to offer benefits to multiple somatic and visceral conditions such as diaphragm palsy, intractable epilepsy, autonomic as well as somatic nerve stimulation for urinary bladder apart from pain [5]. It is important to define PNS to understand

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its efficacy and indications since mechanisms might differ according to the pathophysiology or the approach [5,6].

However, management of peripheral nerve disorders was started with nerve blocks long before the electrical stimulation, soon after the discovery of local anesthesia.

Peripheral nerve blocks (Temporary and diagnostic)

Reversible, temporary nerve blocks with local anesthetic injections have been employed extensively in the diagnostic evaluations of chornic pain syndromes with good temporary relief but with very little reliabiity in prediction of long term outcomes of a permanent ablative procedure [7,8]. Temporary diagnostic nerve blocks could only provide transient pain relief but failed to be prognostic indicators for dorsal rhizotomy, radiofrequency denervation or dorsal root ganglionectomy and surgical procedures like spinal fusion or decompression [9,10] making reliable patient selection for these procedures, difficult.

Predictive value of diagnostic peripheral nerve block by local anesthtic injection:
Temporary peripheral nerve blocks were employed extensively for diagnostic evaluation of low back pain, sciaica, lumbar facet pain and lumbar radicular pain although their predictive value regarding permanent relief following ablative lesions was unreliable [7,8]. North et al. [7] conducted a prospective controlled, blind study to understand the reliability of peripheral nerve blocks to conclude that negative result following a nerve block may have a better predictive value compared to a positive nerve block. Anesthetic blocks relieved sciatic pain when adminstered distal to the nerve or collateral to anatomical source of pain thus making the therapy a non-specific method in localization or diagnosis of a peripheral nerve lesion.

One small randomized controlled trial (RCT) and a number of longitudinal studies reported success in the treatment of low back pain in FBSS using what has now become known as peripheral nerve field stimulation (PNFS) using subcutaneously placed leads in the area of the pain [11-14].

The multiple clinical approaches to the peripheral nerve pain

Several medical, non-invasive, minimally invasive as well as invasive treatments are available to control chronic painful conditions, implicating the complex nature of pain as an intractable problem. Electrical stimulation of the nervous system, both peripheral and central, has been an accepted therapeutic method with or without breaching the dermal layers. Accordingly, minimally invasive transcutaneous and percutaneous stimulation techniques have emerged successful with remarkable advancements in the technology. Peripheral Nerve Stimulation (PNS) is a reasonably less invasive treatment option compared to stimulation of the central nervous system to control pain. Percutaneous Electrical Nerve Stimulation (PENS), by definition, implies the route of administration, distinguishing itself from the Transcutaneous Electrical Nerve Stimulation (TENS), and engages the non-neural elements more than the nerve itself. PNS targets a nerve trunk supplying the painful body parts, to provide relief.

Nomenclature of peripheral nerve stimulation

Several procedures have been declared as PNS or its alternatives with a similar goal i.e. control of pain due to peripheral nerve diseases.

Peripheral nerve stimulation: This is electrical stimulation of a specific nerve (having a specific anatomical nomenclature) that supplies a very distinct part of the body. There is a defined territorial distribution by that nerve and PNS produces changes in the function of the particular nerve. PNS provides unidirectional paresthesia along that selected peripheral nerve with a better stimulation quality [15]. Accordingly, indication for PNS therapy is neuropathic pain along the nerve distribution, so that the stimulation is effective along the affected nerve [16]. This can be achieved by open surgical method, wherein the nerve is exposed, and the electrodes are placed over the nerve or by minimally invasive percutaneous technique. In the latter method, the electrodes are guided via a skin puncture to the desired location of the peripheral nerve that achieves maximum stimulation benefits. In case a specific nerve is not stimulated, the procedure is called Peripheral Subcutaneous Field Stimulation (PSFS).

Percutaneous electrical nerve stimulation (PENS): A combination of TENS, a surface stimulation method and acupuncture (intradermal needle insertion according to Chinese land marks on the body) is PENS. Acupuncture acts by mechanical stimulation but Electro acupuncture (EA) employs electrical stimulation (2-100 Hz) for analgesia mediated through opioid receptors [17]. TENS also can be applied with either low (2Hz) or high (50-100Hz) frequency stimulation on the skin; but not at the same time. At high as well low frequencies TENS produces analgesia by activating smaller motor afferents while high frequency is more selective in stimulating larger diameter a beta afferent to cut down the nociceptor cell activity [18]. PENS delivered via percutaneous insertion of

needles in the vicinity of peripheral nerves, however, utilize both high and low frequencies in a rapidly alternating rhythm to achieve similar effects of stimulation as above [19]. This is particularly useful in patients intolerant to TENS (due to skin irritation or allodynia) and as such avoiding skin resistance, delivers the stimulation to its full potential [20].

Subcutaneous nerve stimulation (SQS): This is implantation of stimulating electrodes in subcutaneous plane for peripheral nerve stimulation.

Peripheral nerve field stimulation (PNFS): Placement of stimulating electrodes, subcutaneously in the affected areas with pain; also referred to as subcutaneous nerve stimulation (SQS). Here electrical impulses from the fascial plane are intended to stimulate the peripheral nerve or its branches in the vicinity of pain and has been reported to be successful in the management of intercostal nerve pain, axial back pain and post-laminectomy pain [11,13]. PNFS/SQS originated from the idea of targeting local peripheral nerve branches in the painful area, some of them being specific peripheral nerve branches, especially when the epidural SCS fails to reach the more distal locations in patients with peripheral nerve injuries or CRPS [13].

The difference between Electro-Acupuncture (EA) or PENS and PFNS is the placement of electrodes for a limited duration of time in the former and permanent implantation in the latter technique. In PENS the needle electrodes are removed after the treatment, which has a limited number of days, similar to acupuncture.

Advancements with PNS

The initial pioneering work of Wall, Sweet and Sheldon continued for 20 years with limited expertise as well as technology [21]. Difficulties were encountered due to ineffective on and off stimulation methods and surgical trauma to the nerves followed by scar tissue formation [22,23]. A percutaneous electrical nerve stimulator was developed by Long in 1973, much similar to the indigenous method of Wall and Sweet, using cordotomy electrodes within 18 G needles, initially for PNS screening but later became more of a prototype for PENS [24]. Percutaneous epidural insertion of cylindrical electrode for epidural and PNS had set in the initiative for minimally invasive procedures by Urban and Nash old in 1982 [25]. A simple and less invasive technique introduced by Weiner and Reid for occipital neuralgia [26] improved the confidence in PNS of occipital and trigeminal nerves [27,28] expanding the gamut of indications, implantation methods and type of electrodes. Further safety and simplification of the technique ensued with ultrasound guidance to place to electrodes for stimulation of any named peripheral nerve throughout the body [29,30]. Trigeminal and occipital nerves remained to be major nerves to receive PNS for a variety of indications like postherpetic neuralgia, trigeminal neuropathy/neuralgia, migraines and cluster headaches [27,31-34].

The minimally invasive nature of PNS increased the indications to relieve postsurgical pain, low back pain, scapular pain, coccydynia and chronic regional pain syndrome-type 2 by placing the stimulator in close proximity to the peripheral nerve [35-38]. As the popularization of PNS continued, evaluation of outcomes and adverse events started to get attention not only to audit the procedure but to refine the technology also [39]. Electrode migrations, fractures, disconnections, erosion of leads and failure of stimulation prompted several modifications [40,41].

Percutaneous electrical nerve stimulation (PENS)

When Wall and Sweet applied temporary electrical stimulation to the infraorbital nerves, they put forth the prototype of PENS [2] similar to the implanted electrodes of Sheldon et al that became models for PNS [42,43]. Placement of electrodes either on the skin or in subcutaneous tissues with TENS, PENS or PNS leads to alterations in blood flow, concentrations of local neurotransmitters and endorphins along with cell membrane polarization thereby inhibiting the nociceptive transmission [44].

For PENS in conditions like back pain, sciatica, diabetic neuropathy, herpetic neuralgia and headache, bipolar needle electrodes are inserted in to tissues for pain relief and removed after the therapy [45-47]. This method combines the simplicity and mechanisms of TENS and EA (Electro Acupuncture) to stimulate the dermatomal sensory nerve endings in order to produce analgesia which is better than TENS and Sham controlled therapy. PENS was also shown to reduce consumption of opioids in a systematic randomized study [45,47]. PENS, however, is very less invasive since it does not require the complex surgical implantation as the bipolar needle electrodes required to stimulate the nerve endings can be removed soon after the therapy. This method does not require great technical skills to administer. Selection of the area of stimulation is also not particularly difficult since the area of sensory impairment is clearly marked out by the patient. Ghoname et al. [44] did a randomized crossover study on PENS to show that the results are superior to TENS in patients with low back pain [45]. PENS has

demonstrated very encouraging, reproducible clinical results in various painful conditions [47,48].

However, the sham treatment results reported was an issue in its accuracy and comments by Cummings probably represent the concerns. Cummings in a review stated that "PENS is neither different in principle nor in practice from EA, and whilst the term accurately reflects the nature of the treatment, there is no substantial justification for referring to PENS as a 'novel analgesic therapy' while the term is acceptable for reporting purposes [49]. This might explain why PENS did not become a popular, sustainable neuromodulation approach even though it is less invasive and temporary.

PENS (and TENS also) was helpful as a trial stimulation for PNS, along with electrophysiological studies and nerve blocks to make better selection of indications [44,50]. Limited success could only be achieved with the extremity pain, especially in the lower extremities until the morphological configuration of the electrodes was altered to a cylindrical percutaneous type, thus reducing the interface with epineurium and minimizing scar tissue formation [28,51]. The refined configurations improved the access to the sensory afferents in head and face regions as well as extremity peripheral nerves.

Wireless Neuromodulation with nanotechnology

A bulky traditional SCS equipment with implantable electrodes enclosed inside a catheter, long extension wires connecting these electrodes to an IPG remains to be an issue. All these components are placed surgically inside the patient body and complications related to the surgical (multiple) procedures as well as the failures of any of these components by default become those of the neuromodulation therapy. Several efforts in industry-perspective intend to reduce the bulk with improved efficiency; mostly IPG related durability and extension of life of the battery. Some of them have been successful but still surgical placement is still a requirement to make all the components to function, including the long tunneling to connect the IPG with the stimulating leads.

A recent advancement in neuromodulation field is the new external wireless power generator (WPG) that applies a dipole antenna for electric field coupling. This is accomplished via 'microwaves' at Giga Hertz frequencies (GHz). This wireless device (currently from Stimwave technologies), instead of lower inductive frequencies between 100-500 kHz, (for most of the implanted medical devices) is powered by a radiative electric field coupling at microwave frequencies via a micro-antenna on the implanted stimulating electrode. Additionally, these waves enable miniature sized implants to be placed significantly deeper in tissues through a needle. The higher frequencies applied afford minimal power loss and also offer superior energy transfer to miniature implants [52]. This phenomenon was earlier mentioned by Feynman as the principle behind the frequency vs wavelength changes in his description of nanotechnology (…there is plenty of room at the bottom) and accordingly skin depth only decreases with square root of the scale ratio (scale on which frequency goes up and wavelength comes down). As he mentioned, superconductors have reduced the resistance in modern physics today [53].

The micro-implant WPG is capable of delivering the range of clinically appropriate stimulation with 800-1350 μm diameter size, a significantly miniature device compared to the conventional SCS-IPG. This is equal to the size of a standard lead body and also includes the nanoelectronics on the device itself. It can be incorporated in to a variety of lead types carrying 4 or 8 contacts either in a percutaneous or a paddle type electrode and the receiver wire is mated to the device internally also transferring power wirelessly (Figure 1).

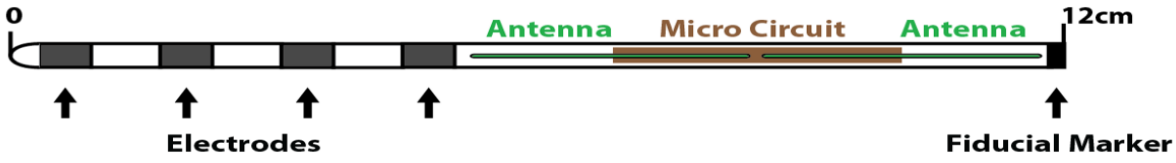

Figure 1: MRI compatible electrode with Nano-stimulator and micro circuit to contact wireless pulse generator. This is the only implantable component required for WSCS.

A dipole antenna receiver intercepts the high frequency microwave electromagnetic energy coming from outside the body to produce an oscillating electric field. Frequency in the range of GHz was found to be more energy efficient [54]. Typically, the antenna within the device lumen can be 2-8 cm long, and can be modified

depending upon the indications and the depth of implantation, since the EMF (electrode magnetic field) energy is dissipated across the tissue layers (of skin, fat, muscle, blood vessels and bone). Deeper the placement, the longer the antenna should be to receive adequate power. Each contact on the electrodes is provided with independent power, a part of an 'application-specific' integrated circuit, as the embedded circuitry within the device enables production of charge-balanced waveforms. This is managed by internalized addressing systems within the device (Figure 2).

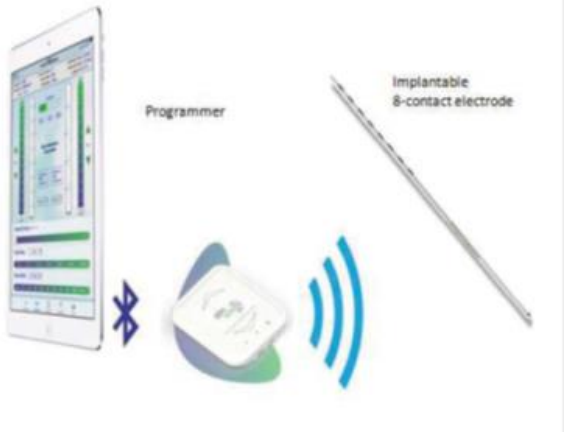

Figure 2: Neurostimulator the contacts on the electrodes are managed by independently integrated, circuits that are application specific. The circuitry system within the device produces charge-balanced waveforms.

It is important to note that microwave fields are safe since the high frequencies fail to activate to cell membranes and thus nervous tissue damage is unlikely. The WPG employs standard cellular phone technology, with an average pulse output power of up to 1 Watt, depending upon the stimulation parameters and according to the requirements of the target tissue. A radiofrequency (RF) transmitter placed inside the WPG encodes stimulus waveforms into the signal according to the program settings. A microprocessor inside this transmitter controls the data communications and settings (Figure 3). Clinicians as well as patients communicate with the WPG via a controller that uses Bluetooth technology and also can be accessed by a software application (app) on a mobile phone [55]. Figure 3 shows the chronic tibial nerve stimulator (CTNS) and the external pulse generator around the calf.

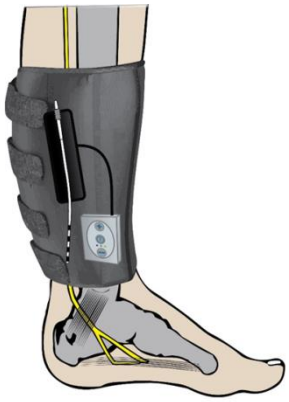

Figure 3: An illustration of the Protect CTNS (Chronic Tibial Nerve Stimulator) System in use. The ankle and neurostimulation device are superimposed to provide the reader with additional perspective.

Discussion

Recent advances in wireless technology facilitated the rapidly evolving stimulator systems while experimental work was providing additional information on peripheral nerve morphology and electrophysiological properties.

Animal models of PNS

Morch et al. [56] have proposed a mathematical model of SQS based on the anatomy of the skin and subcutaneous tissue. The model predicts an optimal implantation depth of 10–15 mm below the skin surface to achieve activation of the greatest area of Aß fibers and the smallest area of Ao fibers. Using a similar computational model, Frahm et al. have found the lowest threshold of Aß fibers when nerve and electrode were in parallel, with currents within therapeutic range (<10 V) of PNFS [57]. Vera-Portocarrero et al. (2013) used rodent models of inflammatory and neuropathic pain to investigate subcutaneous electrical stimulation (SQS) vs. transcutaneous electrical nerve stimulation (TENS) [58]. The rodent model of subcutaneous stimulation was compared to a rodent TENS model, since an argument could be made that SQS is just "TENS under the skin." When comparing both models, there were differences in the effects of each therapy modality on rodent models of neuropathic pain and inflammatory pain.

SQS was effective in the neuropathic pain and had cumulative effects on hyper sensitivity of both inflammatory and neuropathic pains with reduction mechanical hypersensitivity observed on Days 3 and 4, thermal hyperalgesia in first four days and reductions in

cold allodynia observed only in the first day of stimulation. In contrast TENS was effective in the inflammatory model only and tolerance to its antihypersensitivity effects developed with time. These results indicated that SQS and TENS act through difference mechanism of action.

Further characterization was done with the SQS model. The importance of the location of the lead implant was demonstrated by determining that implantation of the subcutaneous lead in the primary area of injury was necessary to have effectiveness [59]. Additionally, the length of stimulation and the amplitude of stimulation influence the amount of effectiveness that SQS has in a rodent model of neuropathic pain [59,60]. Mainly the longer the stimulation and the higher the amplitude, the greater the effectiveness.

These results demonstrate that SQS produces anti-nociceptive effects in rats with nerve injury. Parameter optimization becomes clearly important since in the rodent model, location, length, and amplitude are critical parameters for the effectiveness of SQS. Results point to different mechanism being involved for the effects of SQS and TENS. PNS, as an additional component to SCS in nonresponsive cases of neuropathic back pain, was promising in the earlier studies but could not meet with the safety requirements due to the off -label use of the bulky SCS equipment.

Long term effects of direct current application to peripheral nerves

The experiments were performed in deeply anesthetized rats. The effects were monitored by changes in nerve volleys evoked in epidural stimulated hind limb afferents and in the synaptic actions of these afferents. Both were found to be facilitated during as well as following stimulation of a skin nerve and during as well as following epidural applied current pulses of 5- to 10-ms duration. The facilitation occurring ≤2 min after skin nerve stimulation could be linked to both primary afferent depolarization and large dorsal horn field potentials, whereas the subsequent changes (up to 1h) were attributable to effects of the field potentials. The findings lead to the conclusion that the modulation of spinal activity evoked by DC does not require long-lasting polarization and that relatively short current pulses and intrinsic field potentials may contribute to plasticity in spinal activity. These results suggest the possibility of enhancing the effects of epidural stimulation in human subjects by combining it with polarizing current pulses and peripheral afferent stimulation and not only with continuous DC.

New & Noteworthy the aim of this study was to define conditions under which a long-term increase is evoked in the excitability of myelinated nerve fibers. The results demonstrate that a potent and long-lasting increase in the excitability of afferent fibers traversing the dorsal columns may be induced by synaptic ally evoked intrinsic field as well as by epidurally applied intermittent current pulses. They thus provide a new means for the facilitation of the effects of epidural stimulation. [61].

Direct current (DC) evokes long-lasting changes in neuronal networks both pre-synaptically and post-synaptically and different mechanisms were proposed to be involved in them. Different mechanisms were also suggested to account for the different dynamics of presynaptic DC actions on myelinated nerve fibers stimulated before they entered the spinal gray matter and on their terminal branches. Studies with K^+ channel blocker 4-amino-pyridine (4-AP) on DC-evoked changes in the excitability of afferent fibers stimulated within the dorsal columns (epidurally) and within their projection areas in the dorsal horn and motor nuclei (intraspinally) showed that 4-AP-sensitive K^+ channels contribute to the sustained DC-evoked post-polarization increases in the excitability at the level of terminal branches of nerve fibers but not of the nodes of Ranvier nor within the juxta-paranodal regions where other mechanisms would be involved in inducing the sustained DC-evoked changes [62].

Unlike spinal epidural compartment, peripheral nerve space does not accommodate implantation of the present-day neurostimulator systems and thus has been associated with complications and adverse events [52,63].

Further refinements are necessary to make the PNS more acceptable neuromodulation option, for all its good therapeutic effects.

The wireless technology with its minimalistic design mitigates the mechanical complexity related to the bulky “implantable” components of the traditional SCS equipment. Wireless neuromodulation showed promise in its limited clinical use and paves path to expanding indications for the relief of chronic pain conditions. A significant reduction in hardware associated complications would follow due to the minimally invasive nature of both the technique as well as the technology. A single electrode implantation without the necessity for tunneling and an implanted pulse generator can add comfort to the patient and surgeon while reducing the health care costs, procedure time, postoperative pain, and adverse events to achieve the desired pain control [64].

The wireless SCS system with nanotechnology has been clinically applied for SCS, DRG and PNS throughout Europe and in the USA for several years and multiple trials have shown encouraging results. The capabilities of this system however, enabled its utility to be tested in a variety of chronic pain syndromes. Poon et al [54,65] demonstrated that in a biological media the operating frequency for wireless powered devices was in GHz range as opposed to the MHz could have potential advantages. At this frequency range, the size reduction of the receiver has been demonstrated in their subsequent studies by Tyler Perryman et al, while the tissue depth relationship to the energy transmission were further elaborated [65,66]. Tyler Perryman et al conducted studies in animals and verified the tissue depths at which the wireless stimulation could achieve effective current density [66]. The dipole antenna of the wireless system (at 915 MHz) could energize the stimulators implanted at a depth of 12 cm in porcine models, especially efficient with a 4.3 cm antenna.

In preliminary case studies, Stimwave wireless technology has been reported to be safe and effective as PNS modality in cases of craniofacial pain, occipital neuralgia and post herpetic neuralgia [67-69].

In addition, the minimally invasive technology may be benefit patients with:

a. Compromised immunity as in cases of herpetic neuralgia, retro viral infections, chronic debilitating diseases and malignancy.
b. Comorbid conditions like Diabetes mellitus, chronic renal failure, and anemia.
c. Fragile skin conditions secondary to neuropathy, psoriasis, chronic limb ischemia.
d. Limited life expectancy in painful conditions and those associated with malignancy.

Perspective

From surface electrical stimulation with TENS to implantation of electrodes and power generators, pain management has progressed to a minimally invasive therapy providing significant improvement in disability. PENS and EA (electro acupuncture) despite their ease of application have not been popular in neuromodulation most likely due to the lack of evidence-based literature. PNS on the other hand found increasing acceptance as a preferred method to control intractable pain following the percutaneous technique. However, the technology, being an off -label use of SCS, required finesse and further advancements in terms of its energy delivery as well reduced bulk of implanted material. Wireless neuromodulation with nanomaterials provide the required technological substrate missing in application so far. Initial experience in cases with refractory occipital neuralgia, craniofacial pain and intercostal neuralgia due to herpes zoster has been encouraging.

Further experience in larger groups of patients would be expected to make this wireless stimulation technology to replace the bulky, cumbersome implantation devices in the limited peripheral nerve space.

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