History of Peripheral Nerve Stimulation

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Abstract:

Peripheral nerve stimulation (PNS) is an established neuromodulation approach that has been successfully used for treatment of various painful conditions since early 1960-s. This review provides a comprehensive summary of relevant publications on PNS dividing its history into three distinct periods. The milestones of the field are related to development of procedures, equipment and indications.

As the most rapidly growing segment of operative neuromodulation, PNS continues to evolve as current and emerging clinical indications become matched by basic and clinical research, technological developments and procedural refinements.

Key words: peripheral nerve stimulation, spinal cord stimulation, nerve root stimulation, neuromodulation

Introduction

Whenever a new patient in my practice is considered for peripheral nerve stimulation (PNS) procedure, same questions inevitably come up in conversation with the patient and family, and then again with the referring / primary physician, and finally with the insurance company where the procedure is reviewed – how new and experimental PNS is and how different it is from other neuromodulation approaches. This situation reflects current state of PNS and indicates several important issues. First of all, there is significant shortage of information regarding this approach, partly due to lack of awareness in the medical community at large, and, to a major degree, due to lack of commercial support from device manufacturing companies – in stark contrast with abundance of educational materials for more established neuromodulation approaches of spinal cord stimulation and intrathecal drug delivery. Second, and probably just as important, is the paucity of scientific clinical and basic research work in support of PNS approach, its safety, efficacy, and cost-effectiveness. Last and probably intimately related to the first two issues, is the lack of regulatory approval for PNS as a technical application for existing devices that are used for it in routine practice.

Unfortunately, this situation represents somewhat a vicious cycle – there are no marketing efforts from device manufacturers and distributors due to the lack of regulatory approval, and this approval will never be given unless the manufacturers apply for it. Lack of marketing efforts, low awareness and lack of educational materials have, for a long time, resulted in low volume for this particular device application – and its off-label status and unlikely chance of getting insurance approval made situation worse since low volumes translate into lack of clinical experience and difficulty in collecting sufficient

clinical data to come up with any scientific information that would be needed to get the regulatory approval.

Despite all these hurdles, the field is rapidly developing, and the increasing number of publication regarding use of PNS approach supports its gradual acceptance by the neuromodulation community. Goal of this chapter is to briefly review PNS history and to track the forty some year long path from original introduction to clinical practice to its current state.

Invention of PNS

For many centuries electricity has been used to treat variety of human ailments. Therapeutic effects of electric shocks from torpedo fish were known in antiquity, and pain relief from electrical discharges of this Mediterranean ray was described by Scribonius Largus in patients with gout and headaches. The pain would get better when these patients touch the electric fish or when they put their feet into a pool with torpedo fish [1]. This approach to pain control apparently persisted for a very long time – and there is mentioning of the electric fish used for pain control in early American plantations [2]

A more modern approach to peripheral electrical stimulation was introduced in the beginning of 20th century when a consumer electrical device called Electreat was introduced for treatment of pain and many other conditions [3]. This technology later was translated into a transcutaneous electrical nerve stimulation (TENS) that continues to be widely available today.

Before this, however, was a very interesting description of electricity used for pain

control when directly applied to the peripheral sensory ("sentient") nerve. Julius Althaus in 1859 wrote the following [4]:

> *"a direct reduction of sensibility in a nerve can be accomplished in the following way: if a continuous, or a rapidly interrupted induced current of medium intensity is sent through the trunk of a nerve—say the ulnar, or the sciatic … and the action of the current be kept up for a quarter of an hour or more, the pain which is excited by this proceeding becomes much less, after a certain time, than it was at the beginning of the operation, and a feeling of numbness is produced in the limb. I do not mean to say that sensibility can be entirely destroyed by this local application of electricity, but I am quite satisfied that it is notably diminished by it. The result is much more striking, if there is a morbid increase in sensibility in a nerve, as in the case in neuralgia, than if a nerve in its normal state is acted upon."*

He then went on to describe differential effects of cathodal and anodal stimulation on patients' perception, as well as the effect of increasing frequency of stimulation, up to certain limit, that produces stronger decrease in nerve sensitivity – a surprising depth of observations with mid-19th century technology.

True beginning of the clinical PNS application or treatment of pain started in 1960-s. The creators of "gate-control" theory of pain, Drs. Melzack and Wall, postulated in their article published in 1965 in Science that innocuous sensory information may suppress transmission of pain [5]. Non-painful information is delivered to a secondary afferent neuron (or the first central transmission cell) that also receives information from nociceptive afferents. The same large fibers that carry non-nociceptive information excite

cells in substantia gelatinosa that inhibit transmission of painful signals from the periphery.

Although this theory was based on serious experimental findings, a clinical confirmation was needed to check its validity. In a follow up paper called "Temporary abolition of pain in man" published in 1967 Wall and Sweet demonstrated that non-painful electrical stimulation of peripheral nerve does indeed suppress pain perception in the area that it innervates. In a true spirit of science, they did it by inserting electrodes into their own infraorbital foramina [6].

Later, this was described in a book "Pain and the Neurosurgeon" [7]:

> *"Turning from there animal studies to man, Wall and one of us (WHS) asked ourselves if artificially intense stimulation confined to the low-threshold A fibers could produce clinically demonstrable reduction of pain. We first tested ourselves, using 0.1-msec square waves at 100 cps, sticking into our own infraorbital nerves needle electrodes insulated except for the tip. Tingling, buzzing or vibrating sensations were evoked in some portion of the sensory domain of our nerves at a voltage near the threshold. These were not unpleasant feelings and were always tolerable for an indefinite period. Moreover, we each had analgesia to pinprick in this area of paresthesia during the stimulation. But both the objective sensory loss and our subjective sensations returned rapidly to normal when the stimulus stopped."*

Soon thereafter, an implantable device was created and used in patients with chronic pain [8]. The first PNS surgery was done on a 26-year-old woman with clinical presentation consistent with a complex regional pain syndrome (CRPS) [7]:

> *"On October 9, 1965, Dr. Wall and one of us (Dr. W.H. Sweet) implanted a pair of silastic split-ring platinum electrodes around the ulnar and another pair around the median nerve in the arm carrying the wires out of the skin at the mid-forearm. On the median nerve 0.1-msec pulses at 100/sec and 0.6 volts provoked a pleasant tingling in the lateral three fingers and corresponding hand and stopped the pain in the medial three fingers and hand as well as tenderness in the third finger and palm."*

This quote clearly breaks the myth of PNS being a "novel" modality as its clinical application for treatment of pain preceded, albeit by only a year or two, introduction of spinal cord stimulation (SCS) by Dr. Shealy [9].

PNS Progress: Early Years

The 50-year-long history of clinical use of PNS may be divided into several distinct periods. The first period, a period of semi-experimental PNS use, started with pioneering experience of Wall, Sweet, and others, and lasted for 15-20 years. That was a time when PNS surgery could be done only in few leading centers – primarily due to lack of commercially available equipment. Even before publication of the first series of eight patients with neuropathic pain in whom stimulation resulted in lasting pain suppression as long as the stimulator was "on"[6], Shelden implanted PNS electrodes around mandibular branch of the trigeminal nerve and stimulated them through an implanted receiver at 14 kHz achieving temporary relief of severe facial pain [10].

As the matter of fact, subsequent publications revealed that these implantations were performed as early as in 1962, even before the "gate control" theory of pain was

introduced [11]. Shelden and colleagues in Pasadena, California, operated on three patients with third-division trigeminal neuralgia using a technique “based on nerve depolarization.” Stimulation parameters allowed delivering up to 10 V of electricity at 14.5 kHz using a receiving unit connected to the mandibular division with platinum electrodes. The device was intended to be turned on when the patients experienced their pain attacks at frequent intervals throughout the day. First of these three patients had complete relief of his pain with numbness in the sensory distribution of the stimulated nerve and after several weeks of stimulation experienced prolonged remission and then successfully used the device again when the pain recurred 7 year later. Second patient never used the device and remained pain free form more than 10 years. The third patient was pain free for 5 years but the device malfunctioned when the pain recurred. This was thought to be due to excessive fluid absorption by the Silastic covering of the implant [11].

Over the following 10 years, multiple reports appeared in the literature dealing with various applications of PNS, summarizing experience with various types of equipment, and describing different surgical techniques for PNS electrode implantation. The articles that appeared in 1970-s and 1980-s [12-27], mostly represented single-institution series with use of different electrodes that were implanted in direct contact, or in close vicinity of the peripheral nerve, the same nerve that was thought to be responsible for generation of pain either as a result of direct traumatic or iatrogenic injury, or as a part of CRPS.

Use of “cuff-type” electrodes, later supplemented or replaced by “button-type” electrodes, was generally associated with good outcomes. In most series, good (more than 50%) pain relief was observed in majority of patients. Longer follow up showed decrease

in percentage of patients experiencing significant improvement in pain intensity. For example, Sweet in 1976 [17] reported the overall long-term success rate of 25%, and in 1982, Nashold et al. reported successful outcomes in 53% of patients with upper extremity nerve implants and only 31% of patients with sciatic nerve implantation making a total success rate of less than 43% [24]. The problems, however, included the need in surgical exposure of the nerve to be stimulated and difficulty in achieving adequate positioning of contacts for optimal paresthesia coverage [21]. In addition to this, multiple reports of nerve injury from electrode insertion or stimulation-related fibrosis made PNS less attractive [14,28], particularly since the SCS approach became widely accepted as means of long-term treatment of medically intractable neuropathic pain of various etiologies. Interestingly enough, the very long-term follow up of patients implanted with these cuff electrodes showed that beneficial effects of PNS may last for longer than 20 years in a cohort of patients [29].

To overcome the need in surgical exposure of the peripheral nerve, a percutaneous trans-spinal technique of electrode insertion was developed where a cylindrical electrode was inserted through a downward directed epidural needle and then advanced into the foramen next to the exiting nerve root [30]. The original report suggested using this approach for combination of SCS and PNS, but later this technique was adapted for dedicated spinal root stimulation [31,32].

A wealth of important information was gathered during the first two decades of PNS use. One of the phenomena reported at that time was increased responsiveness to stimulation in some of the stimulated patients. One of the reports noted that about third of PNS patients may reduce amount of stimulation required to relieve pain after 6 months of

stimulation [16]. Patients with peripheral nerve injuries treated with PNS described decrease in their need for stimulation, and this took on average 1 year to occur. The pain relief by then was satisfactory and the stimulator use infrequent [23].

Even during early PNS development, an importance of psychological evaluation and its value in patient selection was clearly identified. In addition to secondary gains, economical and non-economical [15], various psychological and psychiatric conditions, such as depression, conversion disorder, hypochondriasis, and personality disorders were noted to be associated with poor prognosis [24]. It became clear that only formal psychiatric and psychological testing can reveal non-organic issues, such as fear of failure, marital conflicts, financial gain, employment-related conflicts, all of which may affect outcome of the patient's treatment [24].

PNS Progress: Maturation Stage

During the second period, starting in mid-1980-s, PNS was treated as an established surgical procedure. The electrode implantation involved surgical exploration of the peripheral nerve and placement of a flat plate ("paddle"-type) multi-contact electrode immediately next to it. Since these electrodes (such as Resume and Symmix, manufactured by Medtronic, Minneapolis, MN) were already widely used for SCS, there was no need in using cuff-like devices, and introduction of implantable pulse generators rather than previously used radiofrequency-coupled devices made long-term stimulation easier for the patients who did not have to carry an external stimulator and keep attaching the transmitting antennae to the skin above the internal receiver. After first report by Racz and team in 1988 [33] that illustrated details of this approach based on experience

with 2 patients with CRPS type 2 (causalgia) due to electric burns 6 and 3 years earlier, multiple enthusiastic centers worldwide continued using PNS for various neuropathic pain syndromes [34-43], but the relative lack of interest among majority of the implanters resulted in little efforts from the device manufacturers in getting appropriate FDA approval for use of their implantable generators in PNS. Even now, according to the manufacturers' manuals, the only devices specifically approved for peripheral nerve stimulation are radiofrequency systems made by Medtronic (Minneapolis, MN) and neuromodulation division of St Jude Medical (formerly Advanced Neuromodulation Systems, Plano, TX). To make implantation of a paddle electrode next to the peripheral nerve to be stimulated more straight forward, it was suggested to attach a special mesh to the paddle base [44]. This eventually resulted in development of dedicated PNS paddle electrode with mesh integrated into the paddle (OnPoint, Medtronic).

Elimination of cuff-type electrodes resulted in decreasing the risk of perineural fibrosis, but did not make implantation procedure less invasive and the entire process – more conducive for a full-scale pre-implantation trial, similar to what is being done in SCS field. As the matter of fact, the lack of predictability and true testability of the PNS approach was a major obstacle for wide acceptance of the technique. Early on, it was noted that local anesthetic nerve block is not a predictor of pain relief with stimulation [17].

Later, an initial optimism regarding use of TENS in selection of PNS candidates [15] was cooled down by a larger and longer experience of the same group showing that long-term success rate was essentially equal among those who did and did not respond to TENS prior to PNS procedure [19]. Same conclusions were reached by another group of

implanters earlier [14].

Slightly different approach was advocated by Long in 1973 who suggested using a percutaneous electrical nerve stimulator with 18-gauge thin wall needles and cordotomy electrodes for screening of PNS applicability [12]. This practical suggestion, along with the initial experience of Wall and Sweet with infraorbital nerve stimulation [6] may be considered a prototype for subsequently developed separate technique of percutaneous electrical nerve stimulation (PENS) reviewed later in this paper. To the best of our knowledge, however, PENS approach did not become an accepted means of PNS screening although some centers continued using it in regular basis [27].

The main accomplishments of the second period in PNS history was definition of PNS indications and stimulation parameters. Despite some concerns, PNS did not get completely replaced by SCS approach, but remained a preferred option for those neuropathic conditions where a single and relatively easily reachable nerve was thought to be a culprit of pain generation. Larger series of patients with CRPS type 1 (reflex sympathetic dystrophy) [36] and painful nerve injuries [39-42] summarized experience with more than 150 patients and confirmed relatively consistent pattern of long term effectiveness in 55-78% of patients without any major adverse events or complications.

Use of paddle electrodes for PNS application remains an accepted clinical approach. In addition to stimulation of large peripheral nerves in the extremities, paddle electrodes are used for occipital nerve stimulation for treatment of occipital neuralgia and transformed migraines [45-47]. The main benefits of this approach are the unidirectional nature of stimulation as the contacts of each paddle are shielded by insulated plastic base of the paddle, and the lower incidence of electrode migration due to geometry of the

paddle. These very qualities, however, may become disadvantages, as for example in those situations where electrode position requires omnidirectional stimulation. Similarly, higher tissue resistance around paddle electrode provides higher electrode stability but is associated with higher incidence of electrode fractures. Most important issue, however, is the invasiveness of paddle electrode insertion that may be overcome once devices for percutaneous insertion of narrow paddle electrodes become available. An example of this may be an Epiducer device that accommodates a narrow paddle Lamitrode S series electrodes (both manufactured by St. Jude Medical) if it is ever adapted for extraspinal application.

PNS Progress: Percutaneous Era

The most recent, third period in PNS history started with pioneering work of Weiner and Reed [48] that described percutaneous technique of electrode insertion in the vicinity of the occipital nerves in order to treat occipital neuralgia. Although previously described for treatment of occipital neuralgia and various headache disorders [19,23,27], PNS of occipital nerve(s) did not become widely accepted due to discouraging initial results and a cumbersome process of the occipital nerve dissection needed for application of wraparound PNS electrode(s). Weiner's ingenious innovation was in showing that placing PNS electrode in the proximity of the nerve is just as effective for pain relief but also more technically simple and less invasive.

Although percutaneous electrode insertion for PNS was mentioned as early as 1982 by Urban and Nashold when the authors used an epidural needle to reach the contralateral intervertebral foramen and advanced a stimulating electrode toward the selected spinal

nerve [30]. This technique was used in conjunction with SCS but never took off as an accepted modality. But soon after 1999 Weiner's publication, Burchiel and others [49-56] described use of this technique in both occipital and trigeminal areas, and after that the approach was modified by many implanters in term of the electrode type, insertion procedure, indications, etc.

The original PNS indication of occipital neuralgia, both idiopathic and post-traumatic, used by Weiner in a cohort of 13 patients over a 6-year interval (1992-1998), evolved over time and subsequently included so-called cervicogenic headaches [52], pain due occipital neuroma [53] and craniofacial neuropathic pain [50]. Following this flurry of brief mentions, anecdotal reports and preliminary experiences, several larger series and detailed technical reports were published further establishing the practice of PNS with percutaneous electrodes [57-65]. Use of PNS for migraines, suggested by Popeney and Aló [57] based on experience with 25 patients in an uncontrolled study, was supported by subsequent clinical publications [66-69] and in-depth imaging study [70]. Subsequent to that, three neuromodulation device manufacturing companies (Medtronic, St. Jude Medical and Boston Scientific) launched prospective randomized studies to determine benefits of occipital PNS for migraine patients; the high prevalence of migraines in general population and large number of medically intractable cases make this indication potentially largest in PNS applications. In addition to occipital PNS with percutaneous electrodes, occipital PNS paddles [46] and a combination of supraorbital and occipital PNS [68,69] have been tried for migraine treatment and prevention.

A rarer, usually just as disabling, and perhaps much more resistant to medical treatment problem of cluster headaches became another indication for occipital PNS [71-

75]. Here, occipital PNS is an alternative or a complement to hypothalamic deep brain stimulation; and much lower invasiveness with associated lower procedural risks make occipital PNS a preferred or initial surgical modality for cluster headache management. In addition to PNS aimed at occipital nerves, supraorbital PNS has also been tried for cluster headache patients [76].

Supraorbital PNS has been used for variety of indications – originally, it was suggested for ophthalmic post-herpetic neuralgia [54,58] and trigeminal neuropathic pain [50,59,64]. Larger series described use of supraorbital PNS for supraorbital neuralgia [77], and more recently it was tried for migraines [68,69] and cluster headaches [76].

The procedure was not limited to the upper neck and face area – other reports detailed the use of PNS in other parts of the body. For example, percutaneously inserted PNS electrodes were used for control on inguinal pain after herniorrhaphy [78], paraspinal electrodes have been used for treatment of low back pain and sacroiliac pain [79], thoracic post-herpetic pain [80], scapular pain [81], as well as coccydynia [82]. Even the more traditional PNS indication – CRPS type 2 of the arm – has been successfully treated with percutaneous PNS [83]. In addition to that, a concept of stimulating the area that hurts culminated in development of modified PNS technique – subcutaneous neuromodulation targeted at the site of pain [84]. This approach has been refined in treatment of abdominal [85], low back [86-88] and neck pain [88,89]. In addition to percutaneous electrodes, this subcutaneous / epifascial PNS application for localized pain syndromes was recently described with paddle leads as well [90].

Finding peripheral nerve for percutaneous PNS application may be challenging. In cases of supraorbital and infraorbital PNS, this does not seem to be a problem as the

anatomical variability is rather minimal [59]. But in case of peripheral nerves in extremities, it may require real-time ultrasound guidance. After initial cadaver-based evaluation [91,92], this approach was successfully used in clinical practice [93,934]. Moreover, ultrasound guidance was suggested for insertion of occipital PNS electrodes in order to reduce the distance between the stimulating electrode and the targeted nerve(s) [95].

Percutaneous Nerve Stimulation

A slightly different direction that employs similar principle has been explored in last few decades for treatment of pain. If initial experience of Shelden and colleagues [10,11] with implanted electrodes and receivers became a prototype for true PNS, the experiments of Wall and Sweet [6] that used temporary electrodes for temporary suppression of pain may be considered a prototype of so-called percutaneous electrical nerve stimulation (PENS).

PENS treatment is performed with bipolar needle-like electrodes that are inserted into the tissues (as opposed to TENS where electrical stimulation is delivered through the skin) and then removed at the end of treatment session. This approach was used in treatment of low back pain [96-99], sciatica [100], diabetic neuropathic pain [101], and headaches [102,103]. It was also tried in treatment of acute herpetic pain [104] and pain due to bone metastases [105].

Despite thorough analysis of all stimulation parameters (duration, frequency, electrode montage and location) and their effects on treatment results [106-109], PENS did not become widely accepted – although recent introduction of commercially available

PENS apparatus (Algotech Ltd, West Sussex, UK) may change the level of interest to this relatively non-invasive neuromodulation approach.

PNS Progress: Recent Advancements

The newest trends in PNS have to do with new indications, new devices, new techniques and new terminology. As the field of PNS rapidly evolves, all of these aspects translate into large number of publications and research projects stimulating individual investigators and multi-disciplinary collaboration.

One of the most fascinating developments with PNS was discovery of its global pain-relieving effect in patients with fibromyalgia [110-111]. A larger study of this particular indication for occipital PNS is currently underway. A similar study of neuromodulation in fibromyalgia evaluates effects of vagal nerve stimulation (VNS) on this disabling condition [112]. Interestingly enough, VNS procedure that is widely used for treatment of epilepsy and has some potential in treatment of refractory depression, has also been tried for treatment of migraines and cluster headaches [113].

The general trend for lowering invasiveness and reducing surgical trauma became the reason for development of new PNS device that may potentially revolutionize the entire PNS field. Introduced about 10 years ago [114,115], this miniaturized rechargeable stimulation device (Bion, Boston Scientific, Valencia, CA) has been tested in variety of clinical applications. In its current shape and size it was used in treatment of urinary incontinence [116] and subsequently tried for treatment of severe headaches [117,118]. In a series of patients with hemicrania continua, the Bion stimulator provided significant pain reduction (80-95%) in 4 out of 6 patients at the time of latest follow up [117]. A

different group of implanters documented sustained improvement in headache intensity in a majority of patients treated with Bion [118]. Neither report showed any major complication, such as infection, erosion or migration of microstimulator device.

With wider acceptance of PNS in neuromodulation community, multiple reports focused on surgical and device-related complications associated with PNS use [119,120]. The high frequency of electrode migrations, erosions and disconnections prompted development of surgical techniques aimed at minimization of operative mishaps and refining of implantation procedure [121-123].

Finally, the issues regarding exact procedural meaning and variations in PNS spectrum of interventions stirred discussion and controversy. Some of the recent publications address this in a constructive manner [124,125], but there is a good chance that this discussion will continue as newer approaches emerge in addition to or instead of existing traditional interventions.

Conclusion

Despite almost a half-century-long history, PNS appears to be both under-studied and under-utilized in modern neuromodulation practice. As the most rapidly growing segment of operative neuromodulation, PNS will continue to evolve as current and emerging clinical indications become matched by basic and clinical research, technological developments and procedural refinements.

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