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Peripheral Nerve Stimulation in the Treatment of Chronic Pain Syndromes From Nerve Injury: A Multicenter Observational Study

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Introduction: Assessing the feasibility, technical implications, and clinical benefits of peripheral nerve stimulation (PNS) performed by an implantable pulse generator (IPG) located close to the stimulation site.

Materials and Methods: Selected patients were affected by neuropathic pain associated with a documented peripheral nerve lesion, refractory to conventional surgical or pharmacological treatment. A PNS system specifically designed for peripheral placement (Neurimpulse, Padova, Italy) was implanted and followed for six months, recording the degree of patient's satisfaction (PGI-I questionnaire), the pain numerical rating scale (NRS) and the quality of life (SF36 questionnaire), as well as any change in drug regimen and work capability. The statistical significance of differences was determined by the paired Student's *t*-test.

Results: A total of 58 patients were referred to permanent IPG implantation. Stimulation failure due to lead damage or dislocation was noticed in two cases (3.4%) in six months. At the follow-up end, the relative NRS reduction averaged $-58 \pm 30\%$ ($p < 10^{-6}$) and was greater than 50% in 69% of the cases. Quality-of-life physical and mental indices were increased by 18% ($p < 0.005$) and 29% ($p < 0.0005$), respectively. The administration of antalgic drugs was stopped in 55% and reduced in 16% of the patients. Low-energy stimulation was possible in most cases, resulting in an IPG estimated life of 80 ± 35 months.

Conclusions: Successful PNS was achieved with a stimulation system designed for peripheral location. This new technology reduced the incidence of lead-related adverse events and the energy cost of the treatment.

Keywords: Neuropathic pain, numerical rating scale, peripheral nerve stimulation, quality of life, stimulation energy

Conflict of Interest: The authors reported no conflict of interest.

INTRODUCTION

Pain syndromes due to a peripheral nerve lesion often do not respond to conventional surgical and pharmacological treatments and therefore represent a difficult challenge in the clinical practice. In such instances, neurostimulation applied to either the spinal cord or the affected peripheral nerve has generally proved effective in pain management (1–4). However, the optimal approach and interventional technique still remain matter of debates. Spinal cord stimulation boasts a wider clinical experience, but is less selective than direct peripheral nerve stimulation (PNS). Conversely, PNS can entail the disadvantage of an arduous lead positioning, which can further be complicated by a long distance between the pulse generator and the target. In most cases, the stimulator is located in the abdomen or buttocks, even when the nerve to be treated is found in an upper or lower limb (5–7).

The possibility to place the implantable pulse generator (IPG) close to the target might imply a significant improvement in the implantation procedure, avoiding the use of long leads or extensions crossing the joints, which are exposed to mechanical stress and related risk of dislodgement or damage (8–10). This solution might foster a wider clinical use of PNS. A stimulation system specifically designed to this purpose, allowing either surgical or percutaneous lead positioning, is now available in the clinical setting. We report a retrospective review of the patients implanted in the years 2013–2015 in nine different Pain Units in Italy, focusing on both the clinical outcome and the incidence of adverse events in a six months follow-up.

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MATERIALS AND METHODS

All patients suffering from neuropathic pain owing to a peripheral nerve injury of traumatic, iatrogenic, compressive, or ischemic etiology, with or without loss of motor function, persisting for more than six months and not responding to conventional surgical and pharmacological treatment, underwent a PNS trial procedure lasting from 15 to 45 days. Nerve injury was documented by either electromyography (or other neurophysiological tests), MRI, or ultrasound evaluation, when indicated. The diagnosis of neuropathic pain was based on the DN4 standard questionnaire (11). Additional inclusion criteria were a pain degree >5/10 at the numerical rating scale (NRS), age >18 years, patients' ability to provide appropriate informed consent, to undergo follow-up visits and to manage a PNS system. Patients were not considered if nerve injury was not proven, or in case of oncological diseases, blood disorders, systemic or local infection, major psychiatric pathologies, lack of patient cooperation, life expectancy lower than one year, or medico-legal disputes in progress. The authors confirm that the appropriate ethical approval was obtained for this study.

A total of 74 patients entered the trial phase; 43 were males and the mean age was 58 years (range 20–85). The applied stimulation system has been designed to reduce the distance between the electrodes and the IPG (Fig. 1). One or two permanent quadripolar cylindrical leads (Lightline and Fixline models, Neurimpulse, Padova, Italy) were implanted since the beginning of the trial, with no restriction on the anesthesia and placement technique. A percutaneous approach carried out with ultrasound guidance and the use of electrical nerve stimulation, or surgical approach placing the lead on the nerve to be treated after surgical exposure of the nerve was chosen in 48 and 26 cases, respectively. In this stage, an extension was temporarily applied to connect the permanent lead to an external stimulator. The stimulation parameters (pulse rate, width and amplitude, which can be regulated as either voltage or current intensity) were individually set in each patient in order to induce paresthesia. During the trial, changes in the pharmacological regimen were avoided. At the end of this stage, the PNS effect on neurogenic pain was assessed by NRS (12). In case of pain relief of at least 50% of the initial score (58 patients), the extension was removed and the external stimulator was replaced with a permanent IPG, positioned close to the stimulation site (Fig. 2). The IPG models Lightpulse 100, 100L, or 102 (Neurimpulse), all characterized by a small size (11–13 cm^3), were implanted in 18, 37, and 3 patients, respectively. The patient was supplied with a remote control device (Light Helper 100, Neurimpulse), which allowed to adjust pulse amplitude and turn the stimulation ON and OFF, according to the therapeutic needs.

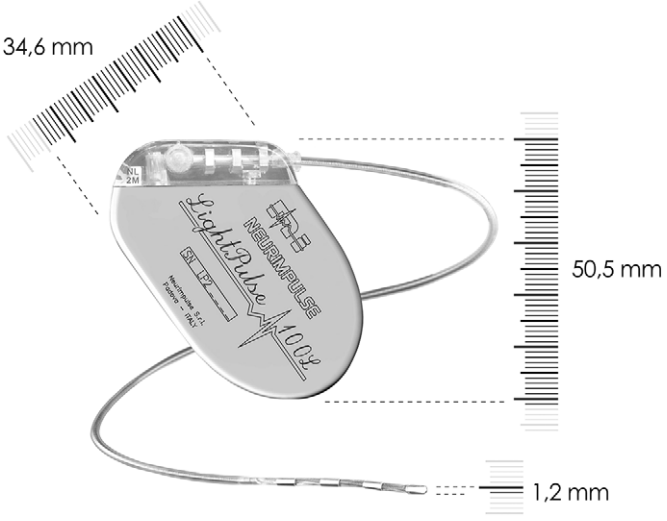

Figure 1. The Neurimpulse Peripheral Stimulation System, comprising the Lightpulse 100L IPG (height and width as shown in the picture, thickness 7.2 mm, weight 25.5 g) and the Lightline lead.

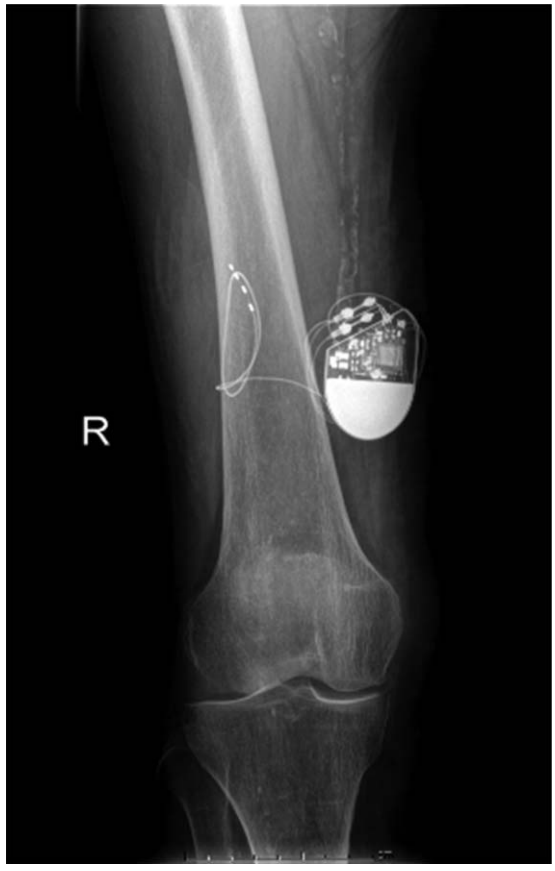

Figure 2. X-ray of an implanted permanent PNS system, featuring a Lightpulse 100 IPG.

The patients were further examined at scheduled visits 1, 3, and 6 months after the implantation of the permanent IPG. NRS index, drug intake, and working ability were recorded preoperatively (baseline) and at every visit thereafter. The degree of personal satisfaction was evaluated by means of the Patient Global Impression of Improvement questionnaire (13) at every follow-up visit. The quality of life was assessed by administration of the standard questionnaire SF-36 (14) at baseline and six-months follow-up. NRS and quality of life determined during the PNS treatment are compared with the corresponding baseline value in each patient. The statistical significance of the changes observed after six-months treatment is evaluated with the paired Student's *t*-test. One or two-samples Student's *t*-test and the nonparametric Wilcoxon rank sum test are applied to unpaired data. The frequency of patients reporting their return to work or a change in drug assumption is expressed as percent of the total sample size. The corresponding significance levels are derived from the *z*-test for a single proportion. Averaged data are presented as the sample mean ± 1 standard deviation.

Table 1. Treated nerves in the Trial and Permanent Phase.

Stimulated nerve	Trial (*n*)	Permanent (*n*)
Trigeminal	4	1
Maxillary	4	4
Mandibular	4	4
Glossopharyngeal	1	1
Greater occipital	3	1
Lesser occipital	1	1
Brachial plexus	16	11
Median	6	5
Radial	3	3
Ulnar	6	5
Posterior brachial cutaneous	1	1
Intercostal	3	2
Femoral	4	4
Sciatic	9	9
Tibial	4	2
C4 spinal root	1	1
L4 spinal root	1	1
L5 spinal root	3	2
Total	74	58

RESULTS

At the end of the trial phase, a NRS reduction of at least 50% was achieved in 58 out of 74 patients (78%), who were enrolled in the second stage of the study (permanent IPG implantation). The stimulated peripheral nerves are listed in Table 1, along with the corresponding number of patients entering the trial and the permanent stimulation phase. The group includes four cases of spinal root stimulation, which was considered as a subtype of PNS since the target was a selected nerve root, not a spinal cord segment. In four patients, the leads were placed on the trigeminal branch responsible for the painful syndrome, with a good result only in one patient. All the implants were voltage-regulated; continuous stimulation was chosen in 45 cases, while the remaining were treated in cyclic mode. The PNS therapy was regularly applied throughout the six-months follow-up in 49 patients. The nine drop-outs (16% of the group selected for permanent implantation) includes one case of lead failure, one migration, five infections, and two patients where the PNS system was explanted due to definitive loss of effectiveness.

The clinical syndromes treated with permanent PNS are shown in Figure 3. Table 2 reports the stimulation parameters and the device expected life based the consumption in the actual operating conditions at six months, in patients implanted with either surgical or percutaneous approach. No significant difference was found between the subgroups, with the exception of the stimulation impedance, which was higher in percutaneous implants. The median pulse voltage was lower (0.56 vs. 0.87 V) and the proportion of patients stimulated at low energy ($\leq$0.5 V) higher with surgical than percutaneous lead placement (Fig. 4). However, none of these differences proved statistically significant with 95% confidence. As a result, the IPG expected life was similar with surgical or percutaneous implantation, ranging from 23 to 148 and 21 to 167 months, respectively. Merging the two subgroups in a single sample yields a mean expected life of 80 ± 35 months with median of 76 months. A service life longer than four years is predicted in 81% of the cases.

Figure 5 shows the frequency distribution of the NRS index at baseline (i.e., before the operation) and at six months PNS, averaging 8.8 ± 1.2 and 3.4 ± 2.4, respectively ($p < 10^{-6}$). The frequency distribution of the individual relative pain modification is reported in Figure 6, including the two cases undergoing removal of the PNS system due to lack of efficacy, who were given a zero score. The mean effect over a total of 51 patients was a percent decrease in NRS of -58 ± 30 in the sample. It can be claimed with 95% confidence that the mean pain reduction in the population is larger than 50%. It is noteworthy that all patients implanted with a permanent IPG featured a PNS-induced reduction in NRS of at least 50% at the

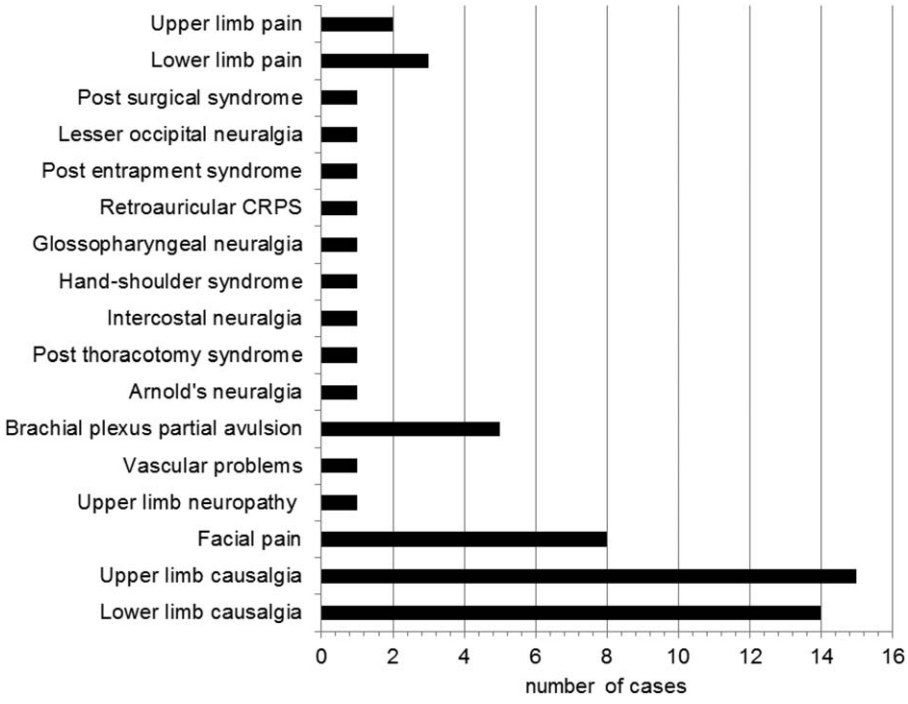

Figure 3. Number of patients per treated pathology.

Table 2. Stimulation Parameters With Surgical or Percutaneous Lead Implantation.

	Surgical	Percutaneous	
Pulse rate (Hz)	34.8 ± 10.5	29.7 ± 11.2	
Pulse amplitude (V)	0.98 ± 0.83	1.09 ± 0.89	
Pulse width (ms)	0.23 ± 0.13	0.24 ± 0.06	
Impedance (Ohm)	410 ± 150	597 ± 405	$p < 0.05$
Expected life (months)	83 ± 34	78 ± 37	

end of the trial phase. At the end of the follow-up, a pain decrease larger than 50% with respect to the baseline was still present in 69% of the patients (35 out of 51). The therapy showed the same antalgic effect in chronic and acute conditions in 50% of the patients, while stronger or weaker chronic effects were reported in 27 and 23% of the cases, respectively. In six patients, no pain relief was demonstrated at the end of the observation period (six months or time of explant: class 0 in Fig. 6). The time-course of the average pain index is represented in Figure 7: the therapeutic effect was already evident at one month and showed no relevant modifications in the later steps. This is further confirmed by the trend of patients' global impression of improvement, which got an average score equivalent to "feeling much better" throughout the follow-up (Fig. 8).

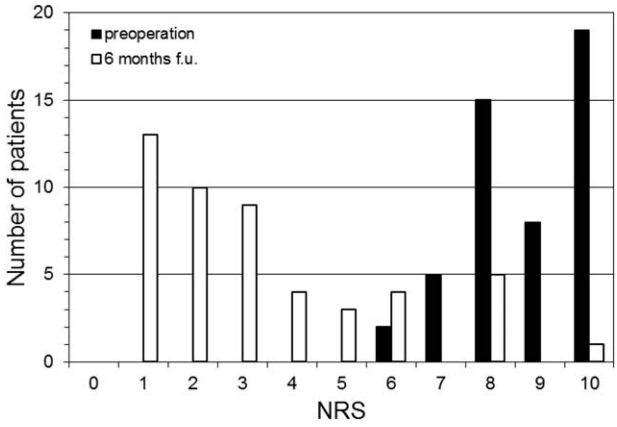

Figure 5. Frequency distribution of the pain intensity, measured according to the numerical rating scale (NRS), before the therapy (filled bars) and after 6 months peripheral nerve stimulation (open bars).

Both physical and mental items of the SF-36 (PCS and MCS) were substantially improved by PNS. If compared with the baseline values, the average PCS and MCS were increased by 18% ($p < 0.005$) and 29% ($p < 0.0005$), respectively. The drug intake was stopped in 55% and reduced in 16% of the patients. The dosage was unchanged in 29% of the cases and an upgrading of the drug therapy was never

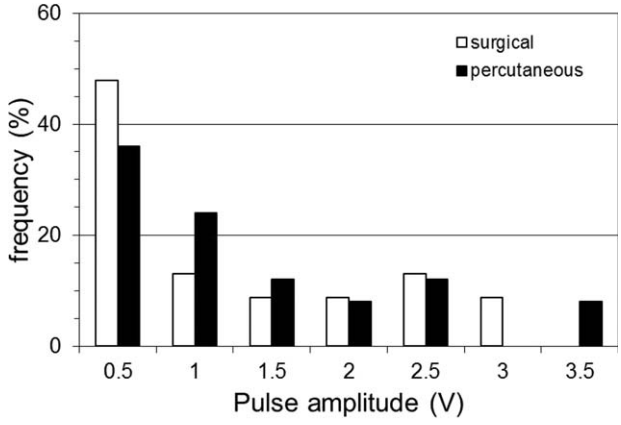

Figure 4. Frequency distribution of the stimulation voltage at 6 months, in patients implanted with surgical (open bars) or percutaneous operation technique (filled bars).

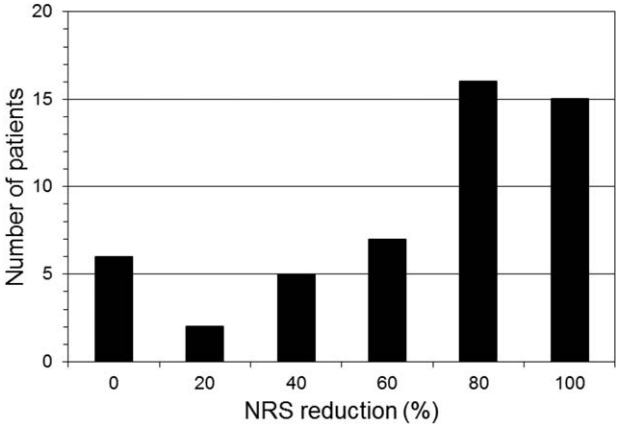

Figure 6. Frequency distribution of the individual pain reduction at 6 months, expressed as percent of the baseline level. Each bin is labeled by the highest value included. Patients in class 0 were nonresponders.

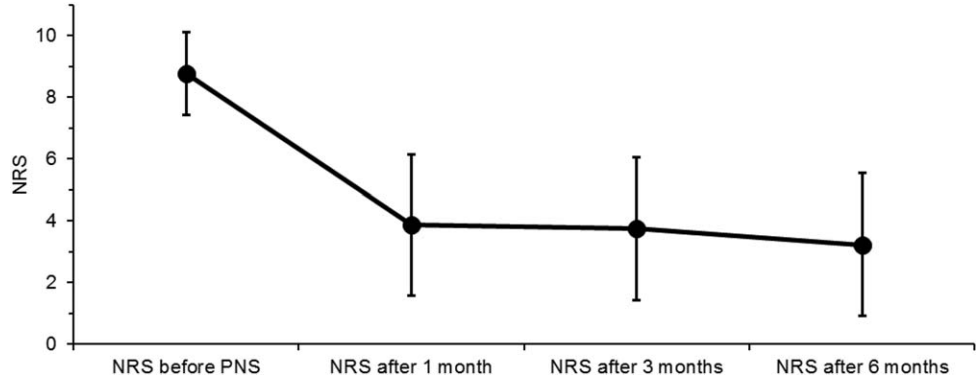

Figure 7. Time-course of the average NRS pain index.

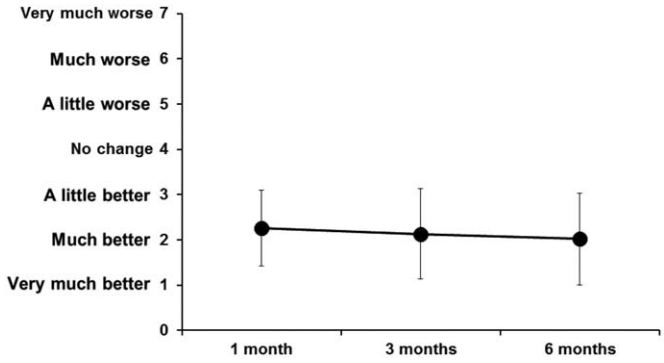

Figure 8. Trend of patients' global impression of improvement.

reported. In the studied group, 15 patients were retired and 34 potentially able to work. Seventeen patients (50%) who did not work before PNS started or restarted a professional activity during the treatment. In the remaining 17 cases (50%), the PNS did not modify the working status: patients who worked or did not work continued working or not working, respectively, while working patients never left their job during the PNS treatment. It is excluded with virtually 100% confidence that the results on either drug intake or work capability could be fortuitous and not related to the therapy (P approaches 0).

DISCUSSION

Our experience confirms the effectiveness and clinical value of PNS applied in patients affected by neuropathic pain, consistently with previous studies (1,4,6). A clear-cut pain relief was obtained, resulting in patient satisfaction and good compliance with the therapy, improved quality of life, reduction in the use of antalgic drugs, and return to work in a relevant proportion of cases. Careful patient selection, including procedures aimed at objectively demonstrating the presence of a nerve lesion, might be crucial to increase the PNS success rate. In the present study, 69% of the patients featured a relative NRS reduction higher than 50% of the basal score after six-months treatment.

In the Pain Centers participating in this registry, all the patients presenting with intractable neuropathic pain (where PNS is indicated as an alternative therapeutic approach) underwent the implantation of a stimulation system consisting of an IPG of small size and a special dedicated lead. Both the lead and the permanent stimulator are designed for a peripheral placement, avoiding the lead extensions generally used with the abdominal IPG location (5,7). This strategy proved effective in reducing the incidence of conductor damage or lead dislodgement, each being limited to 1.7% in six months in the patient group undergoing permanent implantation. Remarkably higher rates of adverse events related to lead failure or instability were reported in previous studies, though the follow-up period was generally longer (7–9,15).

Another advantage of keeping the IPG close to the stimulation target is the reduction of the conductor impedance, which is directly proportional to its length. If the total impedance (comprising the impedance of the lead, the electrodes, and the tissues) is decreased, the same fractional reduction applies to the voltage required to elicit a constant current, by the Ohm's law. As a consequence, the energy of a rectangular stimulation pulse of fixed duration and current intensity, which depends on the ratio of the squared voltage to the impedance, is a positive linear function of the load. The electric charge drained from the IPG battery depends on the pulse energy; therefore, lowering the lead impedance is an undisputed rational approach to the reduction of device consumption, with resulting prolongation of the service life. Based on the actual current drain measured at six months, the expected life of the PNS system used in the present study exceeds four years in 81% of the cases, in spite of the IPG small size.

CONCLUSIONS

Permanent PNS performed by an IPG positioned close to the target nerve has proved safe, reliable, and clinically effective. Avoiding the use of lead extensions and keeping all the system components distal to the joints reduces the incidence of adverse events. A long-lasting therapy can be applied with no need of IPG replacement, thanks to the low pulse energy required to induce analgesia. After the promising indications of this six-months follow-up, further studies are required to confirm the clinical benefits and the good performance of the stimulation system in the long term.

Authorship Statements

Dr. Colini Baldeschi designed and conducted the study and prepared the manuscript. The remaining authors participated in patient enrollment and performed the PNS intervention.

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COMMENTS

This is yet another moderately sized study confirming the efficacy of direct peripheral nerve stimulation. Relevant to the debate surrounding PNS is the utility of dorsal root ganglion (DRG) stimulation. In lower extremity cases, DRG may provide a competitive solution. In the upper extremity, head and neck, this implantable solution may present a very good option especially in terms of its small size, battery life and ease of use.

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This manuscript describes the use of a new peripheral nerve stimulator system in a large clinical series of patients with painful nerve lesions. They limited the patients to those with documented nerve pathology and pain refractory to medical and surgical management. Each patient underwent trial placement, and if adequate analgesia occurred during the trial, they underwent permanent placement. At the 6-month follow-up, 69% of patients maintained at least 50% pain relief. There were improvements in other outcome measures, including patient satisfaction, medication usage, and SF-36 scores.

One of the problems with peripheral nerve stimulation is the lack of commercially-available hardware. Most practitioners adapt spinal cord stimulation equipment for use along the nerves, resulting in the use of extension wires, long tunnels across joints, and high complication rates. The new system described in this report is a dedicated PNS device, designed for use in the extremities. Thus, the leads are designed for either open or percutaneous placement along nerves, the wires are relatively short, the implantable pulse generators are small for use in the confined spaces of the extremities, and the complication rates are relatively low compared to other systems. The authors also provide electrical usage data, suggesting that the relatively short wires contribute to low impedances and increased battery efficiency.

It is encouraging to see the development of dedicated PNS hardware. I hope that this system, and others like it, will begin to fulfill the needs of the patients who are ideal candidates for peripheral neuromodulation.

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The authors summarize multi-center experience with a novel neurostimulation device that is designed specifically for peripheral nerve stimulation (PNS) applications. The series presents a "mixed bag" of indications, stimulated nerves and surgical approaches, but overall results are indeed quite encouraging: the majority of patients (58 out of 74) achieved >50% pain improvement and proceeded with permanent implantation, and almost 70% of those who were followed for 6 months continued to experience same degree of improvement at the time of follow-up.

Although similar in general to the results from earlier reports that used conventional neuromodulation hardware (designed for spinal cord stimulation applications) (1–3), this series presents a set of unique differences. The number of explants and complications was remarkably small; the majority of suboptimal outcomes had to do mainly with indications and/or targets that are known not to respond to PNS rather than technical issues. This is in contrast with the past experience where the technical complications have plagued the PNS field, mainly due to absence of dedicated devices (4).

The ability to place generator in the vicinity of stimulated nerve is indeed very attractive - in the past, the only options we had were either to place the stimulator away from the nerve and cross multiple joints in the process (1,2), or to have a dedicated device that couples implanted receiver and electrode with external source of power (3,5). There were attempts to place conventional PNS generator in the patient's thigh or the calf (6), but introduction of smaller device appears to make this significantly simpler. The device described in this paper has been approved for clinical use in Europe since 2010 (7), it is still not available in the US at the time of this writing. Based on the results of this series, I would hope that this – or a similar – device becomes available to me, my colleagues, and our patients. The need for a dedicated PNS device has been discussed in the past; this series suggests that the answer to our needs is in sight.

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Comments not included in the Early View version of this paper.

