Three-Year Outcomes After Dorsal Root Ganglion Stimulation in the Treatment of Neuropathic Pain After Peripheral Nerve Injury of Upper and Lower Extremities

Michael Kretzschmar, MD, PhD*†; Marco Reining*; Marcus A. Schwarz, PhD†

ABSTRACT

Objectives: Traumatic peripheral nerve injuries (PNI) often result in severe neuropathic pain which typically becomes chronic, is recalcitrant to common analgesics, and is associated with sleep disturbances, anxiety, and depression. Pharmacological treatments proven to be effective against neuropathic pain are not well tolerated due to side effects. Neuromodulative interventions such as peripheral nerve or spinal cord stimulation have generated mixed results and may be limited by reduced somatotopic specificity. Dorsal root ganglion (DRG) stimulation may be more effective in this etiology.

Materials and Methods: Twenty-seven patients were trialed with a DRG neurostimulation system for PNI; trial success (defined as ≥50% pain relief) was 85%, and 23 patients received a permanent stimulator. However, 36-month outcome data was only available for 21 patients. Pain, quality of life, mental and physical function, and opioid usage were assessed at baseline and at 3-, 6-, 12-, 18-, 24-, and 36 months post-permanent implant. Implant-related complications were also documented.

Results: Compared to baseline, we observed a significant pain relief ($p < 0.001$) at 3 (58%), 12 (66%), 18 (69%), 24 (71%), and 36 months (73%) in 21 patients (52.5/14.2 years; 12 female), respectively. Mental and physical function showed immediate and sustained improvements. Participants reported improvements in quality of life. Opioid dosage reduced significantly ($p < 0.001$) at 3 (30%), 12 (93%), 18 (98%), 24 (99%), and 36 months (99%), and 20 of 21 patients were completely opioid-free after 36 months. There were five lead migrations and two electrode fractures (corrected by surgical intervention) and one wound infection (conservatively managed).

Conclusions: DRG neuromodulation appears to be a safe, effective, and durable option for treating neuropathic pain caused by PNI. The treatment allows cessation of often ineffective pharmacotherapy (including opioid misuse) and significantly improves quality of life.

Keywords: Chronic neuropathic pain, dorsal root ganglion stimulation, opioid misuse peripheral nerve injury quality of life

Conflict of Interest: Michael Kretzschmar and Marco Reining were involved in studies organized by Abbott as Investigators (Prodigy I (CRD 694)—A Post-Market Study Evaluating a new Neuromodulation System for the Management of Failed Back Surgery Syndrome or Chronic Intractable Pain of the Low Back and/or Limbs; DELIVERY (CRD 767)—Randomized, Controlled, Single-Blind, ProspEctive, MultiCenter Study Evaluating Anatomic vErsus TaRgeted Lead Placement for BurstDR TherapY During the Trial Evaluation Period; Prodigy MRI (CRD 800)—A Post-Market Study Evaluating the MR Conditional Neurostimulation Systems). Marcus A. Schwarz has no conflict of interest to report.

Address correspondence to: Michael Kretzschmar, MD, PhD; SRH Wald-Klinikum Gera, Department of Pain Medicine and Palliative Care, Strasse des Friedens 122, D-07548 Gera, Germany. Email: michael.kretzschmar@srh.de

* SRH Wald-Klinikum Gera, Department of Pain Medicine and Palliative Care, Gera, Strasse des Friedens 122, D-07548 Gera, Germany; and
† SRH Hochschule für Gesundheit (University of Applied Health Sciences) Campus Gera, Gera, Neue Strasse 30-32, D-07548, Germany.

For more information on author guidelines, an explanation of our peer review process, and conflict of interest informed consent policies, please go to http://www.wiley.com/WileyCDA/Section/id-301854.html

Source(s) of financial support: None.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited; the use is non-commercial and no modifications or adaptations are made.


Copyright © 2021, International Neuromodulation Society.

This is an open access article under the CC BY-NC-ND License (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Peripheral nerve injury (PNI) can be a devastating and life changing event leading not only to functional morbidity, but also to psychological stress and psychosocial deterioration. Advances in surgical techniques have led to improved outcomes; however, 20%-45% patients will still develop chronic neuropathic pain syndromes following an otherwise successful surgical outcome. Pain can result in continued disability and poor quality of life despite recovered motor function (1, 2).

Neuropathic pain is defined by the International Association for the Study of Pain as pain directly resulting from a lesion or disease affecting the somatosensory system (3, 4). Unlike nociceptive pain, neuropathic pain persists long after the injury has recovered (5).

Complex regional pain syndrome (CRPS) is a severe variant of neuropathic pain. CRPS has a constellation of symptoms and is subdivided into two types. Type I (formerly referred to as “Reflex Sympathetic Dystrophy”) is without an identifiable nerve injury, whereas type II (“causalgia”) is the result of a detectable nerve lesion/injury. Symptoms of CRPS I and II can develop immediately after injury or several months later (1). CRPS-I and CRPS-II have almost identical somatosensory profiles, except there is a stronger loss of mechanical detection in CRPS-II. About 80% of patients with PNI had at least one type of sensory gain (6).

First line therapy for PNI is pharmacological therapy including anticonvulsant medications (gabapentinoids) along with rehabilitative or alternative methods such as physical therapy, psychological counseling, and chiropractic care. Opioid medications have demonstrated only mild efficacy, particularly when combined with antidepressants (7).

Neuromodulation interventions also have a role in the treatment of PNI-induced neuropathic pain (8–17). Spinal cord stimulation (SCS) has been used for many years with relative success (18, 19). Neuromodulation of the dorsal root ganglion (DRG) has been shown to reduce neural excitation in vitro (20–22), as well as reduce pain (23). Specifically, the pivotal ACCURATE trial showed DRG stimulation to be superior to SCS in alleviating pain and revealed the specificity, positional stability, and long-term relief associated with DRG stimulation; a combination that is difficult to achieve in other neurostimulation modalities (24).

Recent publications have shown the safety and effectiveness of DRG stimulation in relieving pain and improving function in patients suffering with chronic neuropathic pain (25). However, long-term evidence of effectiveness is lacking. Also, the study of Huysgen et al. (26) was set up to present pooled data up to one-year post-permanent implant as this is the most common follow-up period in published literature. There is an urgent need to collect and analyze long-term data. Herein, we present three-year safety and effectiveness outcomes using DRG stimulation for PNI at a single center.

MATERIALS AND METHODS

A retrospective chart review of patients who underwent DRG stimulation for the treatment of chronic neuropathic pain after PNI was undertaken at a single German center between January 2013 and December 2015. Acquiring additional written informed consent was waived as no additional interventions or patient interaction beyond standard care was performed. Retrospective collection and analysis of patient data derived from standard care procedures without any additional burden for the patient is included in the treatment contract signed by all patients treated in our facility. This practice is in accordance with the recommendations of the responsible local ethics committee.

Criteria for patients who underwent a DRG stimulation trial include age ≥18 years, neuropathic pain distribution, and failure of various pharmacologic interventions to relieve pain. Routine exclusion criteria for DRG stimulation include psychiatric disorders, previous spinal surgery at the intended lead placement level, and other active implantable devices (e.g., implantable cardioverter defibrillator, spinal cord stimulator, peripheral nerve stimulator).

Baseline PNI characteristics were recorded, including pain location, quality of neuropathic pain syndrome (painDETECT questionnaire, PD-Q (27, 28)), pain duration, and prior pain management strategies. Pain intensity was recorded using the Visual Analogue Scale (VAS; 0 = no pain, and 100 = worst imaginable pain). These pain scores and quality of life outcomes (“German Pain Questionnaire” including Pain Index (PIX) (29), the Short Form-12 mental (MCS) and physical (PCS) health composite score (30), and Quality of Life Impairment by Pain Inventory (QLIP) (31)) are routinely collected at all clinic visits, in addition to information about pain condition related medication usage. Opioid medication use was standardized by converting each drug to morphine milligram equivalents (MMEs) per day using CDC validated conversion factors. Medication Quantification Scale version III, as described by Harden et al. (32), was used to calculate annual intake.

Procedures

All procedures were performed under monitored anesthesia care. Anxious patients received midazolam (1-3 mg) in combination with sufentanil (5-10 μg) intravenously as a premedication. The operation field was prepared using standard practice of our clinic. Thereafter, local anesthesia using a 1:1 mixture of 0.75% ropivacaine with 1% prilocaine to the operation field was performed. Leads were placed via an epidural approach, with access gained using standard loss-of-resistance technique. Leads were advanced in an anterograde fashion and then directed into the intervertebral foramen near the DRG using curved styles under fluoroscopic guidance. In most cases, the decision about the level to be stimulated is made intraoperatively based on the results of the test stimulation. In some rare cases, we performed preoperative intraforaminal test injections with local anesthetics. Appropriate lead position was determined through intraoperative device programming to confirm paresthesia overlap with the painful regions.

All patients underwent a five- to six-day period of trial stimulation. Fifty percent or greater pain relief in their primary pain area was considered a successful trial. Patients then received a fully implantable neurostimulator (Axium®, Abbott, Plano, TX, USA) under standard surgical conditions. The device was programmed to generate the best pain/paresthesia overlap and/or optimal pain relief. Patients were able to control the stimulation intensity themselves using the remote control and were encouraged to keep the intensity below the threshold of perception. Patients returned to our aftercare consultation surgery department at three and six months after implantation and every 6-12 months thereafter.

In most cases, opioid withdrawal was achieved by opioid rotation with buprenorphine as a substitute, followed by a gradual transition toward no opioid usage. In some cases, this required additional hospitalization. After successful opioid withdrawal,
gabapentinoids and other antineuropathics as well as the other co-analgesics were gradually reduced.

**Statistics**

Many consider repeated measures analysis of variance (ANOVA) a standard analytical approach for the given experimental design. However, three reasons justify more adequate statistics. First, an ANOVA tests for any possible difference in outcomes without specific assumptions on when outcomes should deviate from the overall mean or not. Because the effects described here are supposed to reduce negative outcome measures consequently over time (not randomly) and the primary results show very strong differences in dependent measures, an overall test of deviation seems inadequate for this analysis. Second, in case of a significant ANOVA result, further analysis needs to be conducted to...
determine the exact nature of the difference. Third, the effect size to evaluate the meaningfulness of deviation—eta square—is rather global as well as less specific to interpret. Our data strongly agreed with the predetermined statistical hypothesis. Therefore, it is appropriate to analyze the single reductions or improvements by t-tests for depended samples and calculate the effect size Hedges’ g from these statistics. Hedges’ g describes the precise differences between baseline and follow-up measures and should be interpreted just like Cohens d, but is additionally correcting for smaller sample sizes. According to the Kolmogorov-Smirnov test, the differences of means of the dependent measures were normal distributed except for a few pain measures. We therefore decided to use a bootstrap procedure based on 1,000 samples for statistical analyses.

The diagrams in this publication illustrate the mean values of the dependent measures (MQS, QLIP, SF-12, and pain) with corresponding 95% bootstrap confidence intervals. Opioid consumption was presented graphically in the form of a box and whisker-plot. The effect sizes (g) were integrated in the graphs. The Bbootstrapping procedure and tests were performed using SPSS 25 (IBM Corp. Armonk, NY, USA).

RESULTS

A total of 27 patients (one patient met the definition criteria for the diagnosis of CRPS II) were trialed with a DRG neurostimulation system. Of these, 23 patients (85%) had a successful trial (≥50% pain relief), and the therapy system was completed by implantation of the neurostimulator in a second procedure. Leads were placed at levels ranging from L1 to S1 for lower extremity pain conditions. Programming parameters were as follows: frequency 20 Hz; pulse width 200-350 ms; amplitude 150-1200 mA. Complete follow up data up to 36 months were available for 21 patients (two patients were explanted within the first year after implantation).

Mean (SD) age was 52.5 ± 14.2 years. PNI was diagnosed in the upper extremity in four patients, and in the lower extremity in 17 patients. Multiple medications classes (non-opioid analgesics, opioids, anticonvulsants, tricyclic antidepressants) and minimally invasive interventions (peripheral perineural infiltrations with local anesthetics and dexamethasone or intraforaminal local anesthetics for diagnostic purposes) had failed in these patients before trialing DRG stimulation. Patient demographics, PNI etiology, injured nerve, pain area, time since injury, lead location, and baseline medications are presented in Table 1.

Only patients with a definite neuropathic pain component (painDETECT questionnaire [PDQ] = 24.9 ± 4.9) were implanted. Mean ± SD pain score on VAS was 55.1 ± 9.8 mm. At three months follow-up, pain (VAS) decreased to 25.2 ± 6.2 mm. This effect persisted at subsequent follow up: 19.1 ± 5.1 mm, 16.6 ± 3.8 mm, and 14.7 ± 2.9 mm at 12-, 24-, and 36 months, respectively (Fig. 1).

Significant improvements in quality of life as measured on SF-12 MCS and PCS were observed at all time points (all p < 0.001).
Mean (range) daily opioid intake significantly declined from 144 (315) MME at baseline to 3 (33) MME 36 months after intervention (Fig. 4). Opioids (mg MME/d) decreased significantly from baseline score of 50.0 ± 8.3 (PCS) at six months, respectively (Fig. 3). These results stabilized over the course of the treatment until 36 months post-permanent implant.

Medication usage decreased significantly. Mean (SD) scores for SF-12 MCS and PCS improved from 42.3 ± 13.2 at baseline to 43.6 ± 4.9 (MCS) and 50.0 ± 8.3 (PCS) at six months, respectively. These improvements were sustained at all later time points. Physical function as measured on QLIP improved significantly from a baseline score of 33.8 ± 3.4 and 36.5 ± 3.8 at 6- and 12 months, respectively (Fig. 3). These results stabilized over the course of the treatment until 36 months post-permanent implant.

We observed five electrode dislocations and two electrode fractures during the follow up (between 2 and 15 months after primary surgery); four leads were replaced during an additional surgery intervention without any complications, three leads could not be replaced (Table 1); therefore, their position had to be changed to a neighboring foramen (this is possible because of the existence of convergent and divergent pathways (22)). Whether the spread of the triggered paraesthesia reached the target region was checked again intraoperatively. In most cases, it was necessary to increase the pulse width to reach the affected area completely. This approach did not influence the pain-relieving effect of the therapy. One patient developed a superficial wound infection which was conservatively treated and controlled. Two patients asked for explant of the device within the first year after complete implantation despite good pain relief under therapy due to subjective discomfort caused by the implant (pocket pain). These patients were eliminated from the analysis upfront.

**DISCUSSION**

Neuropathic pain after PNI is extremely difficult to manage. People with symptoms that persist for at least six months or who have symptoms that last longer than expected for tissue healing or resolution of an underlying disease are considered to have chronic pain. Chronic pain is an emotional, social, and economic burden for those living with it (33). Depression, reduced quality of life, absenteeism from work, and a lower household income are positively correlated with chronic pain. Injury to peripheral nerves often leads to abnormal pain states (hyperalgesia, allodynia, and spontaneous pain), which can persist after the injury heals. Opioid agonists show reduced efficacy against neuropathic pain. In addition to analgesia, opioid use is associated with hyperalgesia and analgesia tolerance, whose underlying mechanisms share some commonalities with nerve injury-induced hypersensitivity (34, 35). Drugs proposed as first-line agents include tricyclic antidepressants (particularly amitriptyline), serotonin-norepinephrine reuptake inhibitors (particularly duloxetine), pregabalin, and gabapentin. Second-line treatments include lidocaine plasters and capsaicin high concentration patches for peripheral neuropathic pain only and tramadol. Third-line treatments include strong opioids and botulinum toxin A (for peripheral neuropathic pain). However, meta-analyses indicate that only a minority of patients with neuropathic pain have an adequate response to drug...
therapy (35, 36); several reasons may account for this, including a modest drug efficacy, a high placebo response, the heterogeneity of diagnostic criteria for neuropathic pain, and an inadequate classification of patients in clinical trials. Improving the current way of conducting clinical trials in neuropathic pain could contribute to reduce therapeutic failures and may have an impact on future therapeutic algorithms (37).

At present, SCS is the most frequently used neuromodulation technique for neuropathic pain from PNI, although peripheral nerve stimulation (PNS) was originally designed for this purpose. PNS appears less invasive than SCS and provides specific target coverage. PNS has been in use for over 50 years to treat patients suffering from chronic pain who have failed conservative treatments; however, reports are rare, and results are conflicting (13, 14). The use of technology developed for other applications in PNS has led to an unnecessary number of device complications and the limited adoption of this promising therapy. Recently, Pope et al. (16) reviewed the potential of PNS for pain in the extremities. Peripheral neuromodulation techniques, either as a stand-alone therapy or as an adjuvant to SCS, may be particularly effective when the pain is localized to a part of a single extremity or when the source of the pain is related to the malfunction of a known peripheral nerve.

SCS is not, however, without limitations and is not a panacea. About 75% of patients have a successful trial, but SCS may only be effective against a limited range of conditions and can provide incomplete pain relief. Furthermore, when SCS is successful in providing analgesia, therapeutic efficacy can fade with time, often due to the loss of paresthesia distribution in the painful area or compensatory spinal plasticity/habituation resulting in loss of therapeutic effect (19). In addition, paresthesia associated with tonic SCS treatment must overlap with the painful regions and establishing paresthesia with SCS can be difficult in axial locations such as the foot (38). These circumstances complicate the treatment of neuropathic pain following PNI with SCS.

Due to this situation, alternative treatment options have long been sought. Spinal nerves, formed from afferent sensory axons (the dorsal root) and motor efferent axons (the ventral root), emerge from the intervertebral neural foramina between adjacent vertebral segments. The DRG is located at both sides of the spinal cord on the distal end of the dorsal root in the lateral epidural space and houses the cell bodies of sensory neurons. The DRG serves as a modulatory area for controlling sensory information originating from both the periphery and cell body to more central neural pathways. It is an active participant in the development of certain forms of chronic pain. Therefore, the DRG might be an attractive target for electrical stimulation (22). In 2011 (Europe) and 2012 (Australia), the procedure of DRG stimulation was approved for use in the treatment of chronic intractable pain and transferred into clinical practice. In 2015, DRG stimulation was approved for use in the United States for patients with chronic intractable pain of the lower limbs associated with a diagnosis of CRPS I and CRPS II (peripheral causalgia).

The body of evidence to support DRG stimulation has been steadily growing (39–42), especially in the lumbar region. There are a few case reports on the use of cervical and upper thoracic DRG stimulation (43). However, long-term results are still very scarce.

Our retrospective chart review illustrates clinically relevant and statistically significant reductions in pain, and improvements in quality of life and physical function in patients with PNI treated with DRG stimulation at 36 months follow-up. Nearly 80% (of the original 27 patients) in our cohort responded well to DRG stimulation, with notably thorough pain relief and nearly 100% reduction in opioid use at 36 months follow-up. Improvements in SF-12 MCS and PCS scores approach those of a normal population (29).

All our patients were cared for at regular follow-up visits. This made it possible to control the consumption of analgesics on the one hand and to assess functionality and quality of life on the other. DRG-stimulation therapy could terminate the originally high dose opioid therapy within 6-12 months. In some cases, opioid withdrawal was only possible under inpatient conditions and required the use of buprenorphine as a substitute. Consumption of co-analgesics also declined significantly, although more gradually. Comparable data from the literature are rare. (44, 45). Systemic opioid therapy for patients suffering from chronic (non-cancer) pain is challenging, as risks and benefits need to be balanced for a therapy that rapidly develops tolerance (46). Alternatively, neuromodulation therapies have high levels of evidence and have been shown to mitigate opioid consumption (47). This is notable because the effectiveness of the drug therapy in neuropathic pain is rather poor and use of opiate medication for this indication often leads to misuse and dependence (48, 49).

As part of the aftercare, we routinely administered SF-12 and QLIP questionnaires to our patients. Both physical (PCS) and mental component (MCS) summary scales improved significantly. This was also accompanied by an improvement in a more functional (quality of life impairment by pain) scale. Our results regarding these parameters are comparable with those of Morgalla et al., who treated 34 patients with chronic inguinal pain after hernia surgery with DRG stimulation and followed them up over three years (50).

The number of complications observed in our retrospective analysis is consistent with the data of the pool analysis by Huygen et al. These authors identified pain at the IPG pocket site (10.2%), lead fractures and migrations (11.8%), infections (5.1%) (26) as the most frequent complications. This rate may appear relatively high; but, it must be taken into account that this was still a young and technically completely new therapeutic procedure (41). With increasing experience and further improvement of the hardware, a reduction in the complication rate can be expected.

Our outcome data, in terms of improvements in efficacy over time, are remarkable in comparison to SCS therapy. A recent review revealed that in 20%-40% of SCS patients, the initial effectiveness declines, due to a central nervous system tolerance (51, 52). This loss of efficacy is the leading reason for eventual system explantation (53). The pathophysiological mechanisms underlying our findings can currently only be speculated, and it is likely that multiple mechanisms are responsible. The main analgesic effects of SCS involve activation of the descending pain inhibitory system (54). Taghipour et al. suggested that the stimulation of the dorsal column neurons would result in release of neurotransmitters in the dorsal horn by the efferent fibers from periaqueductual gray matter (PAG), rostral ventromedial medulla (RVM) and Raphe nuclei as a mechanism of chronic antinociceptive effects of SCS (55). According to Uno (56), the following mechanisms are likely to involve chronic antinociceptive effects of SCS. In the neuropathic pain condition, disinhibition of the dorsal horn circuits appears to enable Aß fibers to access to the lamina I neurons. Antidromic impulses of Aß fibers activated by SCS excite lamina I neurons in the dorsal horn, which drive ascending nociceptive control system such as PAG/RVM.

DRG stimulation has emerged as a promising therapy for the primary sensory neurons of the DRG, which are target sites for PAG.
the pathophysiologic changes that lead to neuropathic pain (57). The DRG contains the somata of the primary sensory neuron (PSN). Several reviews have outlined the importance that the PSN plays in the development and maintenance of chronic pain (21, 22). The PSNs also contain a T-junction where the distal and primary axons combine with a stem axon that connects to the soma. This junction within the pseudounipolar neurons acts as a junctional failure point for the central projection of sensory information. It also serves as a modulatory area for controlling sensory information originating from both the periphery and cell body to the more central neural pathways (58). The influence of the supra-spinal effects of DRG stimulation on cognitive pain processing are also recognized (59, 60). A recent study with laser-evoked potentials has shown that DRG stimulation may even result in restorative processes, by normalizing the transfer of pain signals from the periphery to supra-spinal levels (61). Ultimately, all of these mechanisms of action are completely different from those of electrical SCS.

Although this study provides insight into the potential use of DRG stimulation in PNI, there are several limitations. This was a single-center investigation analyzing outcomes from one provider and approach. Although this may help limit discrepancies in methodology, patient environment and previous treatments were not standardized. In addition, this was a retrospective report of 27 cases, in which the data relied on accurate-patient information and record-keeping. Lastly, our study consisted of a limited patient pool of only 21 individuals with three-year outcome data. Our limited observations suggest that neuromodulation of the DRG may have a positive effect on PNI-associated neuropathic pain. This technique may be a valuable option for patients suffering from otherwise intractable pain.

CONCLUSION

Results from this retrospective chart review contribute to the growing body of evidence to support DRG stimulation as an effective, targeted treatment option for patients suffering from PNI-induced neuropathic pain. Our three-year outcomes show sustained improvements in pain, function, and quality of life, and these are observed shortly after device implantation. Furthermore, patients are able to reduce or eliminate their consumption of expensive, often ineffective, and potentially life-threatening medications. Physicians should work with the patients with goal-oriented follow-ups assisting the reduction in medication consumption.

Authorship Statement

Michael Kretzschmar performed all procedures. The data collection from the medical records was performed by Michael Kretzschmar and Marco Reining. Marcus A. Schwarz performed the statistical analysis. Michael Kretzschmar prepared the manuscript with input from all authors; all authors discussed the results and provided critical feedback.

How to Cite This Article:


REFERENCES

COMMENT

Dorsal root ganglion (DRG) stimulation has literally revolutionized the field and given neuromodulators the ability to treat a variety of conditions that we were never able to consistently treat before (i.e. post herniorrhaphy, pelvic pain, amputee pain, etc.). With the evidence on Cervical DRG being so limited, this is a welcome addition to the constantly growing body of literature on this therapy. More importantly, this manuscript continues to demonstrate the overall efficacy of DRG stimulation with strong real-world data.

Corey Hunter
New York, NY USA