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Dorsal Root Ganglion Stimulation in Chronic Painful Polyneuropathy: A Potential Modulator for Small Nerve Fiber Regeneration

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ABSTRACT

Objectives: Neuromodulatory treatments like spinal cord stimulation and dorsal root ganglion stimulation (DRGS) have emerged as effective treatments to relieve pain in painful polyneuropathy. Animal studies have demonstrated that neurostimulation can enhance nerve regeneration. This study aimed to investigate if DRGS may impact intraepidermal nerve fiber regeneration and sensory nerve function.

Materials and Methods: Nine patients with chronic, intractable painful polyneuropathy were recruited. Intraepidermal nerve fiber density (IENFD) quantification in 3 mm punch skin biopsy was performed 1 month before DRGS (placed at the level of the L5 and S1 dorsal root ganglion) and after 12- and 24-month follow-up. Quantitative sensory testing, nerve conduction studies, and a clinical scale score were also performed at the same time points.

Results: In 7 of 9 patients, DRGS was successful (defined as a reduction of ≥ 50% in daytime and/or night-time pain intensity), allowing a definitive implantable pulse generator implantation. The median baseline IENFD among these 7 patients was 1.6 fibers/mm (first and third quartile: 1.2; 4.3) and increased to 2.6 fibers/mm (2.5; 2.9) and 1.9 fibers/mm (1.6; 2.4) at 1- and 2-years follow-up, respectively. These changes were not statistically significant ($p = 1.000$ and 0.375). Sensory nerve tests did not show substantial changes.

Conclusions: Although not significant, the results of this study showed that in most of the patients with implants, there was a slight increase of the IENFD at the 1- and 2-year follow-up. Larger-scale clinical trials are warranted to explore the possible role of DRGS in reversing the progressive neurodegeneration over time.

Clinical Trial Registration: The Clinicaltrials.gov registration number for the study is NCT02435004; Swiss National Clinical Trials Portal: SNCTP000001376.

Keywords: Dorsal root ganglion stimulation, intraepidermal nerve fiber density, nerve regeneration, painful polyneuropathy, spinal cord stimulation

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

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INTRODUCTION

Polyneuropathy is typically characterized by sensory symptoms in the distal parts of the limbs, such as sensory loss, paresthesia, and sharp, shooting, and burning pain.[1,2] Etiologies for polyneuropathy are numerous, including diabetes mellitus (DM), alcohol abuse, treatment with toxic agents like chemotherapeutic drugs, nutritional deficiencies, autoimmune-mediated causes, and hereditary factors. In up to 50% of cases, an underlying cause cannot be identified.[3–5] In recent decades, the prevalence of polyneuropathy, which ranges from 1% to 3%,[1,3,6] is increasing because of an aging population and the increasing prevalence of risk factors such as DM and obesity.[3,7,8]

Disorders of sensory nerve function in polyneuropathy are diverse and depend on the type of afferent nerve fibers that are affected.[9] Most polyneuropathies affect both small and large nerve fibers and are therefore termed mixed fiber neuropathies.[10,11] Small fiber neuropathy (SFN) is defined as a structural abnormality of small nerve fibers with the degeneration of the distal intraepidermal terminations of small-diameter myelinated A_δ and unmyelinated C sensory nerve fibers.[12–14] Typically, SFN is a distal, symmetric neuropathy with patients experiencing symptoms in a length-dependent pattern, in a stocking-glove distribution, starting in the feet and ascending proximally to the ankles and even above the knees, and later affecting the hands.[15] Large fiber neuropathies (LFN) result from dysfunction of the large A_β fibers that mediate vibratory and touch sensation[2] and are characterized by loss of joint position, loss of vibration sense, and sensory ataxia.[16,17] Nerve conduction studies are a sensitive and specific method of assessing LFNs but do not allow the measurement of the small nerve fiber function. Somatic functional assessment of small nerve fibers is achieved by assaying the psychophysical sensory thresholds (eg, cold, heat) by quantitative sensory testing (QST), whereas structural assessment is performed by skin biopsy.[18] Skin biopsy with intraepidermal nerve fiber density (IENFD) quantification is not only considered to be the diagnostic gold standard for assessing SFN.[15,19–22] However, it is also a useful biomarker to assess disease progression by variation of IENFD longitudinally,[23,24] because skin biopsy can be repeated in time with minimal discomfort for the patients. SFN is known to be a progressing disease, and IENFD normally decreases over time.[23]

Polyneuropathy is often underdiagnosed and undertreated.[1] Among several reasons, a relevant one is the fact that pharmacologic treatment is frequently not effective and is accompanied by side effects.[25,26] Neuromodulatory treatments like spinal cord stimulation (SCS) and dorsal root ganglion stimulation (DRGS) have emerged as effective treatments to relieve pain in painful polyneuropathy.[27–39] The dorsal root ganglion (DRG) is an appealing site for neurostimulation as it represents the sensory gateway to the spinal cord, containing sensory neuron somata for all sensory modalities and fiber types: not only the non-nociceptive A_β cell bodies (stimulated with SCS) but also the A_δ and C-type nociception related cell bodies.[40,41]

An effect of neurostimulation on peripheral nerve regeneration after nerve injury has been suggested by previous studies in animal models, and 1 study also suggested an effect of percutaneous neurostimulation on nerve regeneration between the proximal and distal nerve stumps in diabetic rats.[42–45] Therefore, we hypothesized that neurostimulation for pain treatment at the level of the DRG might also lead to intraepidermal nerve fiber regeneration in SFN. The primary aim of this study was to assess the impact of DRGS treatment in chronic, intractable painful polyneuropathy in the limbs on the pathologic progression of clinical confirmed SFN, comparing IENFD by skin biopsy at baseline and after 1 year of treatment with DRGS. Furthermore, with this study, we aimed to quantify the impact of DRGS on sensory nerve function, evaluated by nerve conduction studies, QST, and the total neuropathy score (TNS).

MATERIALD AND METHODS

Patients' Enrollment

Inclusion criteria were age ≥ 18 years and diagnosis of chronic, intractable painful polyneuropathy, either small fiber or mixed fiber neuropathy in the lower limbs, based on typical clinical signs and symptoms,[1] supported by skin biopsy and/or nerve conduction studies. Eligible patients had a pain intensity of ≥ 5 on the numeric rating score (NRS) (ranging from 0 to 10) for at least 3 months, and previous drug therapy (including at least antidepressants and/or alpha-2-delta agonist) was unsuccessful. Key exclusion criteria were coagulation disorders, life expectancy of < 2 years, addiction to drugs or alcohol, and severe foraminal stenosis at the expected target level for DRGS lead implantation. Blood tests were undertaken to screen for common etiologies of polyneuropathy as part of the standard diagnostic work-up of patients with polyneuropathy in our Neurology Department.

This study was based on the same patients as in Koetsier et al[31] and approved by the ethics committee of the Canton Ticino, Switzerland. All patients provided written informed consent before participation in the study. The study was registered at the Swiss National Clinical Trials Portal (SNCTP000001376) and ClinicalTrials.gov (NCT02435004).

DRGS Lead Implantation

The procedure of DRGS lead implantation was previously published.[31] In short, DRGS was delivered by the Proclaim™ DRG Neurostimulator System (manufactured by St Jude Medical, now Abbott, Sunnyvale, CA, USA). Between two and four quadripolar percutaneous DRGS leads were placed in the lateral epidural space at the level of the L5 and S1 DRG, depending on the dermatomal area of pain.[46–48] For the trial phase, the leads were connected by extension leads to an external pulse generator. The trial was defined to be successful if there was a reduction of ≥ 50% in pain intensity and if the patient was expressing a desire to be implanted with an implantable pulse generator (IPG). The average trial stimulation phase was eight (SD = 2) days. In the subjects with a successful trial, the extension leads were removed, and the leads were connected to an IPG. Post implantation device programming proceeded according to standard practice by employees of the device company in collaboration with the hospital staff. Device programming settings were adjusted for paresthesia to overlap the painful areas. After programming, the amplitude was reduced to remain subthreshold but therapeutic.

Skin Biopsy

The patients underwent a skin biopsy within 1 month before the start of the study and after 12 and 24 months. As previously described,[49–51] a 3 mm punch skin biopsy was performed at the ankle site (10 cm proximal to the lateral malleolus) on the body side with more prominent clinical symptoms, if not symmetrical. To

provide information about non-length-dependent neuropathy and the extension of axonal degeneration, 4 of 7 patients who were implanted underwent an additional 3 mm punch skin biopsy at the thigh (10 cm above the knee) at the same time points.[49] Skin samples were fixed in periodate-lysine-paraformaldehyde 2% fixative and sent to the laboratory.

Intraepidermal Nerve Fiber Density Quantification

An immunofluorescence assay to visualize intraepidermal nerve fibers was performed as previously described.[50,51] Briefly, at least three nonconsecutive 50 μm thin skin sections were incubated overnight with the primary antibody against the panaxonal marker protein gene product 9.5 (PGP 9.5, Abcam, Cambridge UK, 1:1000 rabbit, polyclonal). The day after, sections were incubated with fluorescently tagged secondary antibody (Goat Anti-Rabbit, Jackson ImmunoResearch, West Grove USA, 1.700) for 90 minutes at room temperature, and cell nuclei were counterstained with 4′,6-diamidino-2-phenylindole dihydrochloride (DAPI). Sections were analyzed under an inverted fluorescence microscope (Nikon Eclipse Ti-E, Tokyo, Japan) and the IENFD was quantified according to published standard protocols.[52,53] The number of PGP 9.5 positive nerve fibers crossing the dermal-epidermal junction was counted and divided for the length of the section. At least 3 sections were counted, and the average was expressed as "number of fibers/mm." Skin biopsies were rated by a qualified and experienced operator blinded to experimental conditions. Pathological IENFD was defined based on published normative data for distal leg adjusted for age and sex.[49]

Nerve Conduction Studies

Sensory and motor nerve conduction studies were performed in the lower limbs according to published standardized protocols.[54] In particular, peroneal, tibial, and sural nerves conduction velocities, amplitude, and distal latency were measured in all patients included in the study, before DRGS implantation and after 1-year follow-up.

QST

A specially trained research associate performed QST, to determine cold detection threshold (CDT) and warm detection threshold (WDT). The measurement was performed, with stimulation "on", on the dorsal site of both feet in case of implantation at the L5 DRG and on dorsal and plantar site in case of implantation at the L5 and S1 DRGS. Measurements were performed with the Medoc Pathway (Medoc, Israel) device with a cutaneous thermode (square surface-active area 30 × 30 mm) in a quiet office while maintaining a constant, comfortable temperature. Cold detection was defined as the highest temperature at which patients can detect a cold stimulus. Warm detection was defined as the lowest temperature at which patients can detect a warm stimulus. For each threshold, four series of increasing intensities were given at random intervals. CDT and WDT were determined as the mean of the four measurements. The baseline was set at 32 °C, and the temperature was decreased at a constant rate of 1 °C/s until patients perceived the thermode as cold. The temperature was increased at a constant rate of 2 °C/s until patients perceived the thermode as warm. The lower cutoff value was 20 °C, and the upper cutoff value was 50 °C. We considered 1.2 °C in mean temperature to be an important difference.[55,56]

TNS

The TNS is a clinical scale that encompasses symptoms, signs, nerve conductions, and QST and is a validated measure of peripheral nerve function.[57] We used the first 7 items of the scale referring to symptoms and neurological signs to grade the gravity of the polyneuropathy.

Statistical Analysis

Baseline characteristics of patients were described using mean and SD, or as median and first and third quartile in case of normally and skewed continuous variables, respectively, and as count and percentage for categorical variables. Ankle IENFD values were summarized at baseline and 1- and 2-year follow-up as median and first and third quartile. TNS item scores and QST cold and hot detection thresholds were summarized at baseline and 6- and 12-month follow-ups. We used the Wilcoxon signed-rank test to test paired within-patient changes. Ankle IENFD values, TNS item, total scores, and QST cold and hot detection thresholds were compared between follow-up moments and baseline. Additionally, at 6- and 12-month follow-ups, we tested differences in QST cold and hot detection thresholds between DRGS on and off. Associations between the change in pain intensity over the first 12 months of follow-up, changes in IENFD values, and changes in the sum of TNS item scores were computed using the Spearman rank correlation. All these analyses were performed using data of patients still implanted with a device unless stated otherwise.

All statistical analyses were performed using R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). p Values of ≤ 0.05 were considered to indicate statistical significance. We used available cases for all analyses.

RESULTS

Demographics and Clinical Data

Between September 2016 and January 2019, we evaluated 31 patients with intractable painful polyneuropathy at our institution; 9 met the criteria for inclusion and accepted the DRGS lead implantation. Patient characteristics and the efficacy of DRGS in these patients were previously published.[31] A total of 6 (66.7%) were male, the mean age was 63 years (SD 8.7), and the median duration of pain was seven years (range, one to 20 years) at the time of inclusion. All patients included in this study were diagnosed with SFN, which was classified as being length-dependent in all 8 patients in whom skin biopsy was performed. Seven were additionally diagnosed with large fiber axonal polyneuropathy. The etiology of polyneuropathy was various: painful diabetic polyneuropathy (PDPN) (3 patients), idiopathic (3 patients), chronic inflammatory demyelinating polyneuropathy (2 patients), chemotherapy-induced peripheral neuropathy (1 patient). The DRGS trial phase was successful in 8 of 9 patients, and 7 were implanted with an IPG (Fig. 1). At six months follow-up, 6 of these 7 patients showed stable treatment success (defined as a reduction of ≥ 50% in daytime and/or night-time pain intensity) and an improvement in the patient's global impression of change. Additionally, pain extent was reduced, and the impact of pain on functioning and mood was improved significantly.[30,31] The stimulation settings were previously published.[31] The frequency was mostly set at 20 Hz. All patients used the stimulation continuously, except 1 patient who turned the device off at night, having no pain at night.

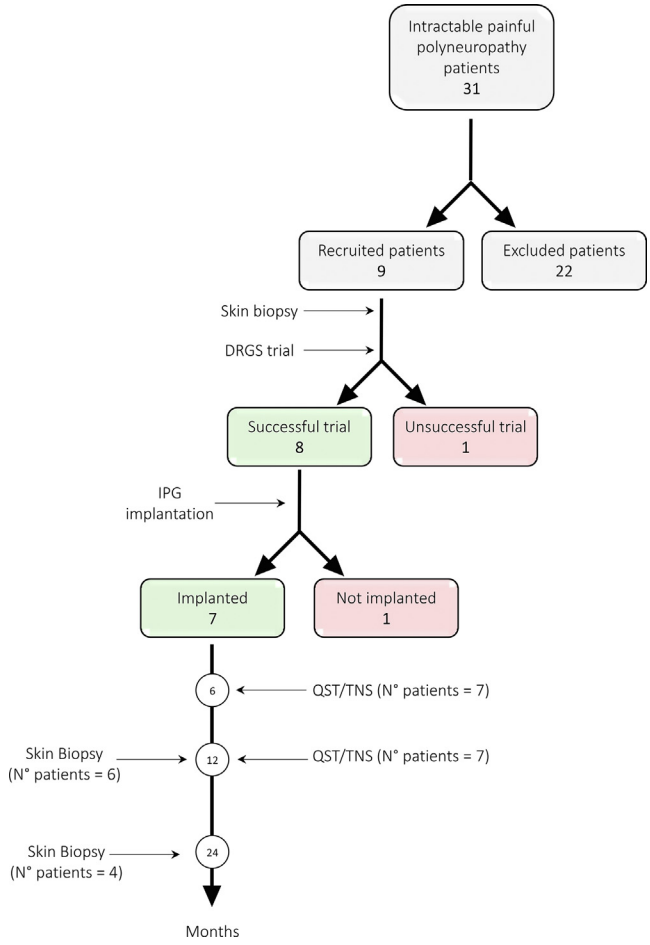

Figure 1. Flowchart of the study design. Schematic representation of the study design and patient's population.

IENFD Changes After DRGS Implantation

Skin biopsies were collected in 8 of 9 participating patients. In 1 subject, a skin biopsy was not performed because of a high risk of skin infection because of uncontrolled DM and lymphedema. The median baseline IENFD among those (still) implanted was 1.6 fibers/mm (first and third quartile: 1.2; 4.3) and increased to 2.6 fibers/mm (2.5; 2.9) and 1.9 fibers/mm (1.6; 2.4) at 1- and 2-year follow-up, respectively. These changes were not statistically significant ($p = 1.000$ and 0.375). At 1-year follow-up, 4 (66.7%) patients with implants improved on their IENFD compared with baseline. Of those with a biopsy available at a 2-year follow-up ($n = 4$), 3 (75%) had a higher IENFD than their baseline value. Figure 2a shows an immunofluorescence staining with anti-PGP 9.5 and DAPI of the ankle skin in healthy control (left) and patients with SFN (right); on the bottom, magnification shows nerve fibers crossing the dermal-epidermal junction (pink dotted line). Figure 2b shows the change in ankle IENFD values per patient over a 2-year follow-up and the high degree of heterogeneity in baseline IENFD values. Of interest, the thigh IENFD decreased in all 4 patients at 1-year follow-up and at 2-year follow-up in the 2 patients who had the biopsy available at that time.

DRGS Implantation Did Not Influence TNS and QST Scores

Table 1 lists the median and first and third quartiles of baseline and 6- and 12-month TNS items. No significant changes, compared with baseline, were detected at follow-up moments. Figure 3 shows individual trajectories of the sum of TNS item scores over time. Differences between the sum of TNS item scores at baseline and six months and between baseline and 12 months were not statistically significant ($p = 0.202$ and $p = 0.292$, respectively).

Cold and warm detection thresholds assessed with QST did not substantially change over 12 months of follow-up (Table 2). None of the differences between six and 12 months, on the one hand, and baseline values, on the other hand, were statistically significant. Furthermore, we did not observe significant differences at six and 12 months between the device being on or off, both for hot and cold thresholds and left and right sides (p values ranged from 0.375 to 1.000).

IENFD and Clinical Scores

The median change in pain intensity between 12 months and baseline was −3.9 points on the NRS (first and third quartile: −5.8; −1.1). We found a strong but insignificant, positive correlation between the change in pain intensity and the change in IENFD values (Spearman's rho: 0.70, $p = 0.233$). A weaker positive correlation was found with a change in the sum of TNS item scores (rho: 0.37, $p = 0.497$). There was a weak correlation between the change in IENFD values and the change in the sum of TNS item scores (rho: 0.25, $p = 0.658$).

DISCUSSION

This is the first study that assessed the impact of DRGS treatment on the pathologic progression of clinically confirmed SFN, comparing IENFD by skin biopsy at baseline and after 1 ($N = 6$) and 2 years ($N = 4$) of DRGS treatment. The results of this study showed that in most patients with implants, there was a slight increase of the IENFD at 1-year and 2-year follow-ups. However, this increase was not statistically significant. The natural process of SFN is progressive axon loss, resulting in the loss of the IENFD over time.[23,58] For instance, in a study of patients suffering from SFN with low-normal IENFD associated with axonal swellings ($n = 15$), IENFD decreased significantly during 19 months.[58] Moreover, Khoshnoodi et al[23] compared the rate of IENFD loss over time in 52 patients with idiopathic SFN (iSFN, $N = 25$), impaired glucose tolerance-associated SFN (IGT-SFN, $n = 13$), and DM-associated SFN (DM-SFN, $n = 14$), to ten healthy controls. Despite a relatively stable clinical course, there was a significant IENFD decrease at follow-up in all three neuropathy groups, whereas there was no change in the control group. IENFD decreased over time in all patients at a similar rate, and the mean yearly rates of IENFD change over time at the distal leg, distal thigh, and proximal thigh were −1.42, −1.59, and −2.8 IENF/mm, respectively.[23] In our study, the IENFD at the thigh decreased in all patients at both time points, following the literature data. This is of particular interest because the anatomical region of the thigh, where the biopsy was performed, corresponds to the dermatomeric region innervated by L3 dorsal root ganglia, at which level no DRGS leads were implanted.

Although the natural process of SFN is a progressive axon loss, the clinical course of SFN is known to be relatively stable.[20,23,59,60] Flossdorf et al[60] studied patients with iSFN ($n = 16$) for an average follow-up period of 5.3 years, and the clinical and

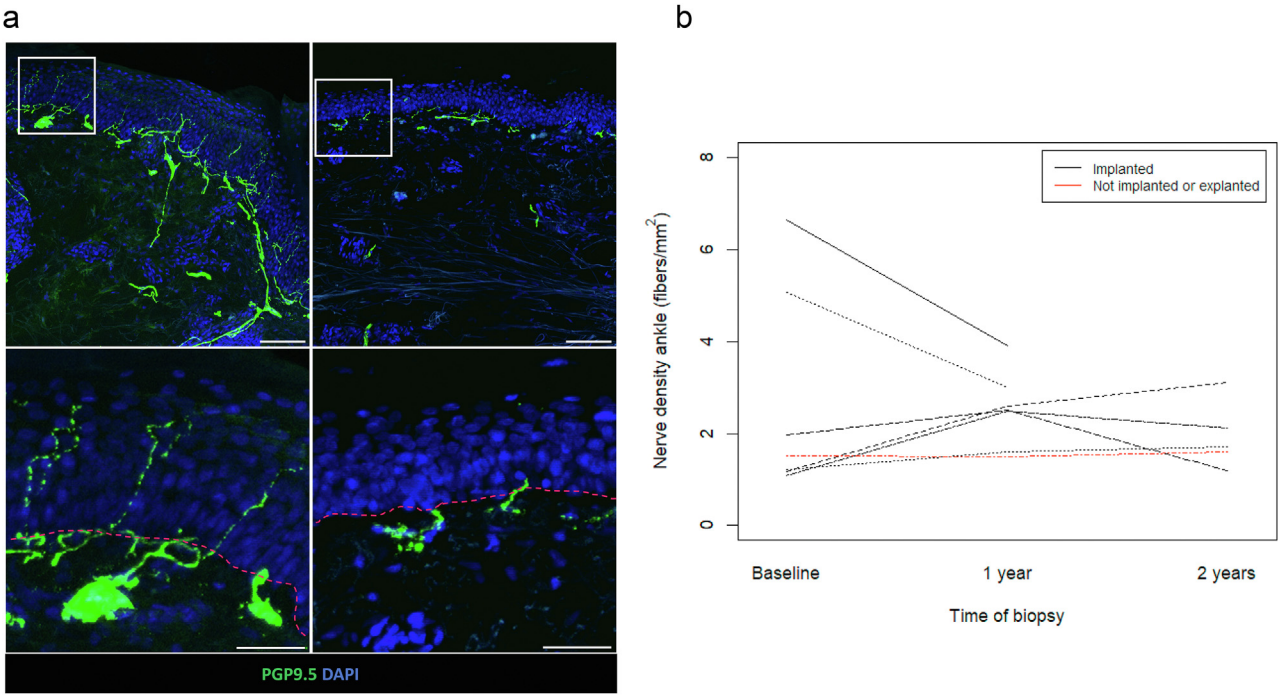

Figure 2. Ankle intraepidermal nerve fiber density at baseline and at 1- and 2-year follow-up. a. Immunofluorescence staining with anti-PGP9.5 and DAPI of ankle skin in a healthy control patient (left) and SFN patients (right); on the bottom, magnification showing nerve fibers crossing the dermal epidermal junction (pink dotted line). Scale bar 50 μm. b. The graph shows for each patients the ankle IENFD at baseline and after 1- and 2-year follow-up.

electrophysiological course remained stable in 75% of patients. Furthermore, MacDonald et al[59] described the clinical course of patients with SFN (n = 110) with an average follow-up period exceeding six years and confirmed the overall stable clinical course of SFN with their study. The correlation between IENFD and symptoms is believed to be nonlinear.[23] Nevertheless, our results show a strong, but not significant, positive correlation between change in pain intensity and change in IENFD values. A weaker correlation was found between the change in pain intensity and the change in the sum of TNS item scores.

Electrical stimulation can increase the speed and success rate of nerve repair by directly promoting axon growth and can increase the activity of Schwann cells and the secretion of neurotrophic factors, as recently demonstrated in a DRG and Schwann cell co-culture *in vitro* model.[61] Furthermore, animal and human studies have demonstrated that peripheral electrical stimulation of the proximal stump of an injured peripheral nerve enhances nerve regeneration, even if the mechanisms remain relatively poorly understood.[43,44] There is also increasing evidence that noninvasive electrical stimulation promotes neuroregeneration and neural repair after spinal cord injury.[62] However, the daily requirement of long-duration peripheral electrical pulses is a practical issue for many patients.

The precise spinal mechanisms of action of SCS are still unknown but originally emerged as an application of the Gate Control Theory of Pain of Melzack and Wall.[41,63] This theory states that electrical

Table 1. Summary of Total Neuropathy Score Items at Baseline and at 6- and 12-Month Follow-Up.

TNS item	Baseline	6 mo	p Value‡	12 mo	p Value†
Sensory symptoms	2.0 (1.8; 2.3)	1.5 (1.0; 3.0)	0.890	2.5 (1.0; 3.0)	0.572
Motor symptoms	0.0 (0.0; 0.3)	0.0 (0.0; 0.0)	1.000	0.0 (0.0; 0.3)	0.851
Autonomic symptoms	0.0 (0.0; 0.0)	0.0 (0.0; 1.0)	0.149	0.0 (0.0; 1.0)	0.346
Pin sensibility	2.5 (1.0; 3.0)	2.0 (1.0; 3.0)	0.851	2.0 (1.0; 2.0)	0.586
Vibration sensibility	2.0 (1.0; 3.0)	1.5 (1.0; 3.0)	0.854	2.0 (1.0; 3.0)	0.932
Strength	1.0 (0.8; 1.0)	0.0 (0.0; 1.0)	0.174	0.0 (0.0; 0.3)	0.089
Tendon reflexes	2.0 (1.8; 3.3)	2.0 (2.0; 3.0)	0.100	2.0 (2.0; 2.5)	1.000
Sural media amplitude (μV)-	3.5 (0.4; 5.5)			3.5 (1.0; 4.5)	0.371
Motor peroneal ankle media amplitude-	2.1 (2.0; 2.9)			2.7 (1.1; 4.4)	0.877

Data are presented as median (first and third quartile).
‡p Values for difference between baseline and 6-month follow-up.
†p Values for difference between baseline and 12-month follow-up.
-Too few observations for estimation at 6-month follow-up.

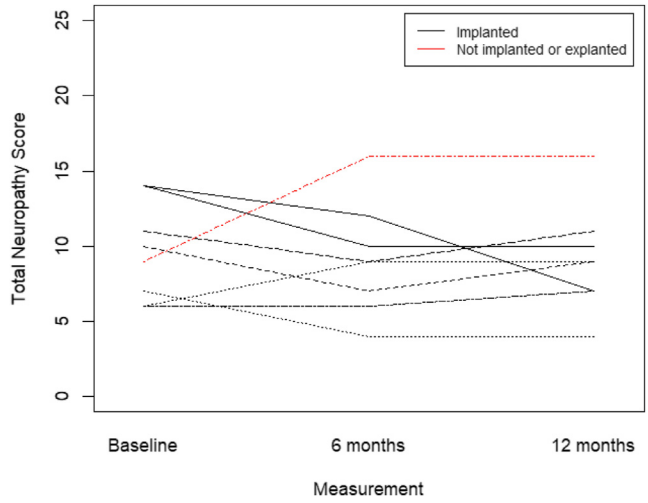

Figure 3. TNS at baseline and at 6- and 12-months follow-up. The graph shows the individual trajectories of the sum of TNS item scores over time at baseline and after 6- and 12-month follow-up.

stimulation of the large myelinated non-nociceptive A_β fibers in the dorsal column of the spinal cord activates the inhibitory interneurons to release gamma-aminobutyric acid in the dorsal horn of the spinal cord. This leads to an inhibition ("closing of the gate") of the spinal nociceptive signal from smaller diameter nociceptive A_δ fibers and C fibers to the brain.[41,63] SCS is, additionally, known to induce orthodromic activation of a supraspinal network inhibiting the incoming nociceptive signal at spinal levels by descending tracts,[41] and decreasing connectivity between sensory and limbic areas,[64] resulting in a reduction of the affective component of pain. Moreover, there is evidence that SCS causes peripheral vasodilatation relieving ischemic pain and improving peripheral blood flow.[65–68] Considering the vascular mechanisms involved in PDPN pathology, it is expected that improved blood perfusion of tissue leads to better functioning of nervous tissue in patients with PDPN.[68,69] A decreased sympathetic outflow during SCS is believed to cause this vasodilatation.[70–72] Furthermore, peripheral vasodilatation during SCS is mediated by the antidromic release of calcitonin gene-related peptide (CGRP) through activation of predominantly small unmyelinated C fibers but also of CGRP positive A_δ fibers.[73,74] The release of CGRP from the free nerve endings and the decrease in noradrenaline release from sympathetic fibers results in peripheral vasodilation. It is likely that the vasodilating effect of SCS also occurs with the application of DRGS. Moreover, animal studies have shown sympathetic fibers to sprout into the DRG after peripheral nerve injury, thereby forming abnormal connections with sensory neurons.[75–77] Because it is reasonable to assume that this sympathetic fiber sprouting into the DRG also occurs in patients with SFN, the DRG might be an even better target for neurostimulation than the dorsal column in patients with SFN.

This study has several limitations. First, it was conducted with a relatively small number of patients with heterogeneity of etiologies of polyneuropathy. The fact that the TNS scores and cold and warm detection thresholds did not improve significantly over time may be caused by a lack of statistical power for these outcomes in our study. Second, although quantification of IENFD in skin biopsies is a

Table 2. Summary of QST Values at Baseline and at 6- and 12-month Follow-Ups.

Measure	Location	Baseline	6 months, DRGS on	6 months, DRGS off	P-value[‡]	12 months, DRGS on	12 months, DRGS off	P-value[†]
CDT (°C)	L5, left	20.0 (20.0; 22.4)	20.0 (20.0; 26.6)	20.0 (20.0; 20.9)	0.310	20.0 (20.0; 21.4)	20.0 (20.0; 24.1)	1.000
	L5, right	20.0 (20.0; 20.0)	21.4 (20.0; 26.8)	24.3 (20.0; 27.5)	0.078	22.0 (20.1; 22.2)	20.8 (20.0; 26.4)	0.125
WDT, mean (°C)	L5, left	46.0 (44.6; 47.5)	43.1 (42.0 (46.6)	45.0 (44.1; 45.1)	0.529	43.7 (43.3; 46.8)	46.4 (44.6; 49.2)	1.000
	L5, right	43.4 (43.2; 46.9)	44.0 (43.3; 45.2)	46.6 (41.9; 46.7)	0.529	42.0 (42.8; 44.6)	44.9 (43.4; 49.7)	0.584

Data are presented as median (first and third quartile).
[‡]*p* Values for difference between baseline and 6-month follow-up, DRGS on.
[†]*p* Values for difference between baseline and 12-month follow-up, DRGS on.

reliable objective measure, QST, and partially also TNS, depend on the active subjective cooperation and attention of the patient and is thus open to bias.[15,53,78,79] Moreover, a limitation of the study is related to the fact that patients with severe polyneuropathy were included, and a rapid progression because of the underlying pathology is possible. Future experiments controlling for the stability of polyneuropathy may improve overall outcomes, including nerve fiber regeneration.

To conclude, the results of this study showed a non-significant trend toward nerve regeneration in SFN with DRGS treatment. Larger-scale clinical trials are needed to prove nerve regeneration in SFN with implantable systems like SCS and DRGS.

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Authorship Statements

Eva Koetsier, Giorgia Melli, Paolo Maino, and Sander M.J. van Kuijk designed the study. Eva Koetsier, Elena Vacchi, Paolo Maino, Jasmina Dukanac, Giorgia Melli, and Sander M.J. van Kuijk conducted the study, including patient recruitment and data collection. Sander M.J. van Kuijk conducted the data analysis. Eva Koetsier prepared the manuscript draft with important intellectual input from Elena Vacchi, Paolo Maino, Jasmina Dukanac, Giorgia Melli, and Sander M.J. van Kuijk. Eva Koetsier and Jasmina Dukanac had complete access to the study data. All authors approved the final manuscript.

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COMMENTS

The authors show in patients with small fiber neuropathy that there is possible nerve fiber regeneration after DRGS. This is an exciting

observation. A significant change is probably not achieved due to the (too) small number of patients studied. Nevertheless, this observation is worth sharing.

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The approach of the study is highly interesting. Unfortunately, the number of patients studied is relatively small and the results are not significant. Therefore, the conclusions of the authors seem somewhat daring to me. Although the title of the manuscript is emphatically cautious, the authors allow themselves to be tempted into some speculation. The discussion contains many interesting details from the literature and reveals the authors' profound knowledge of the literature. The reviewer would have liked at least the question of "why" for the unclear result regarding the hypothesis (pain relief undertreatment was apparently good) to be asked and answered tentatively. Polyneuropathies (of different genesis) are often progressive pathologies. Thus, the worsening of the primary disease may have a corresponding negative influence on the result of the examination or may prevent regeneration altogether. The hypothesis is clearly presented, the results found cannot confirm this hypothesis with certainty at present. I agree with the authors that a broader clinical investigation of the hypothesis is needed to bring the still unresolved but clinically very relevant question closer to an answer.

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This article by Koetsier et al is well written with an extensive reference to the relevant body of literature. It compliments well the earlier manuscript published in Neuromodulation on the same material (Koetsier et al 2020). Moreover, the authors should be rewarded for the precision in method and diligence in the description of the same. Clinical research aimed at understanding the connections between neuropathological findings, pathophysiology and clinical outcomes are rare and of interest to the pain field at large, and possible even beyond. However, the number of study subjects are very small with various underlying aetiologies of polyneuropathy. Conclusion to the role of dorsal root ganglion stimulation in nerve regeneration can therefore not be drawn, but the study may serve as a valuable asset in informing future studies in term of method and statistical power.

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