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Severity of Neuropathy Is Associated With Long-term Spinal Cord Stimulation Outcome in Painful Diabetic Peripheral Neuropathy: Five-Year Follow-up of a Prospective Two-Center Clinical Trial

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OBJECTIVE

Evidence from prospective studies for long-term treatment efficacy of spinal cord stimulation (SCS) in painful diabetic peripheral neuropathy (PDPN) is not available. We report prospective data on the effect of SCS on pain ratings, treatment success and failure, and complications during a 5-year follow-up in patients with PDPN.

RESEARCH DESIGN AND METHODS

Patients with PDPN (*n* = 48) were included in this prospective multicenter study. The Michigan Diabetic Neuropathy Score (MDNS) was used to assess the severity of neuropathy. Numerical rating scale (NRS) score for pain, Patient's Global Impression of Change (PGIC), and treatment success (50% reduction of NRS score or significant PGIC) during 5 years of follow-up were evaluated. Complications of SCS were reported, and associations between baseline characteristics and SCS trial success or failure during a 5-year follow-up were investigated by using survival analyses.

RESULTS

Treatment success was observed in 55% of patients after 5 years. Median duration of SCS treatment was 60 months (minimum 1 month, maximum 60 months), and 80% of patients with a permanent implant still used their SCS device after 5 years. Higher MDNS was associated with treatment failure during the 5-year follow-up (hazard ratio 3.9 [95% CI 1.3–11.6]; *P* = 0.014).

CONCLUSIONS

SCS is successful in reducing chronic pain symptoms in the lower extremities of patients with PDPN up to 5 years after initiation of treatment. Furthermore, 80% of patients with PDPN still use their SCS device after 5 years. Moreover, the severity of neuropathy is associated with a higher chance of long-term treatment failure during a 5-year follow-up.

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Painful diabetic peripheral neuropathy (PDPN) is a progressive neurological disorder accompanied by neuropathic pain symptoms in up to 25% of patients with diabetes (1–4). These painful symptoms have a major impact on health-related quality of life and functional ability (5,6). Pharmacological treatment of PDPN often has only a limited effect and may be accompanied by unacceptable adverse effects (7–9).

In 1996, spinal cord stimulation (SCS) was suggested as a last-resort treatment modality for PDPN (10). SCS efficacy in PDPN has since been confirmed in two randomized controlled clinical trials (11,12). These studies demonstrated treatment success percentages of 59% (13 of 22 patients) and 62.5% (25 of 40 patients) after 6 months and showed that conventional SCS can result in significant additional pain relief compared with best medical treatment in patients with PDPN. Prospective data from controlled trials supporting long-term treatment efficacy of SCS beyond 24 months of follow-up in PDPN currently are not available (11–13).

In 2012, prospective follow-up data on SCS in complex regional pain syndrome type 1 (CRPS-1) showed that 63% of patients still use their SCS device after 12 years (14). However, a large proportion of patients with CRPS-1 (59%) experienced <30% pain relief at the last follow-up measurement compared with initial pain scores. Furthermore, 51 of 84 patients with CRPS-1 (61%) had to undergo one or more interventions as a result of complications during the 12-year study period. Having <50% pain relief after 1 week of trial, SCS was associated with long-term treatment failure in CRPS-1 (14). In failed back surgery syndrome (FBSS), two randomized controlled trials of SCS with 24 and 36 months of follow-up reported substantial pain relief in 58% and 47% of patients, respectively (15,16). Complication rates of SCS in FBSS have been shown to vary from 3 to 81% (17). No patient-related predictive factors for SCS-induced pain relief up to 24 months in FBSS currently have been identified (18), and no predictive factors for long-term treatment failure have been reported.

In PDPN, a complex interaction among hyperglycemia-related mechanisms, vascular-related mechanisms, and loss of neurotrophic support is responsible for damage to the nervous system and development of painful symptoms (19–22). In contrast to FBSS and CRPS-1, PDPN follows a distinct progressive distal to proximal course. Furthermore, PDPN is characterized by primary deficits in small unmyelinated fibers followed by involvement of thicker myelinated fibers (23). SCS has been shown to be ineffective in progressive PDPN, with severe loss of vibration and joint position sense (10), indicating that neuropathy has progressed to involve larger myelinated fibers. Therefore, PDPN-specific scores that are based on nerve fiber functioning should be assessed in prospective cohort studies to provide insight into the predictive value of the underlying pathophysiological process on long-term SCS outcome in PDPN. The Michigan Diabetic Neuropathy Score (MDNS), which is based on abnormal nerve conductions and neurological examination, is a validated assessment of the severity of neuropathy in patients with PDPN (24).

We report the effect of SCS in 48 patients with PDPN on pain ratings, treatment success and long-term treatment failure, and complications during a 5-year follow-up. Furthermore, we analyzed associations between baseline characteristics and SCS trial stimulation success or failure during the 5-year follow-up.

RESEARCH DESIGN AND METHODS

Study Design and Patients

This study was designed as a prospective multicenter clinical trial that assessed SCS treatment success, treatment failure, and complications in patients with PDPN of the lower limbs. The severity of neuropathy was classified by using the MDNS. Before inclusion, all patients were treated according to international guidelines (8,9,25) on the basis of the treatment algorithm of Jensen et al. (7). The total study population comprised two separate prospective cohorts of patients with PDPN with identical inclusion and exclusion criteria, which have been described previously (11,26). Inclusion criteria were as follows: insufficient pain relief and/or unacceptable adverse effects with drug treatment and pain present for >12 months, with a mean numerical rating scale (NRS) score of pain intensity during the day or night of ≥5. The first cohort comprised 15 patients (26) and the second, 33 of 36 patients (1 who died after attempted trial stimulation, and 2 control subjects who did not want to cross over to SCS treatment after 6 months) (11). The follow-up study was performed at Maastricht University Medical Centre+ (MUMC+) and included data on patients from the outpatient pain clinics of the MUMC+ and Radboud University Medical Centre (UMC). The study was approved by the medical ethics committees of MUMC+ (Maastricht, the Netherlands) and Radboud UMC (Nijmegen, the Netherlands).

Trial Stimulation and Follow-up

Implantation of the SCS octapolar lead (Octad lead; Medtronic, Minneapolis, MN) was performed by using local anesthesia and antibiotic prophylaxis as previously described (11). After a trial stimulation period of 2 weeks, the spinal cord stimulator (Synergy Versitrel or PrimeAdvanced; Medtronic) was implanted if the NRS score for pain intensity during the day or night for the last 4 days of the trial period was at least 50% lower compared with baseline or if the Patient's Global Impression of Change (PGIC) score was ≥6 ("much improved" or "very much improved") for pain and sleep. If trial stimulation was unsuccessful, the stimulation lead was removed. Only patients with successful trial stimulation were included in the current study follow-up.

Baseline Characteristics

Baseline characteristics and PDPN history were obtained from all patients with a permanent implant, including duration of diabetes, duration of painful symptoms, NRS score for painful symptoms, type of diabetes, height, weight, age, sex, glycohemoglobin (HbA_{1c}), and MDNS, depending on the number of abnormal nerve conductions and neurological examination (0 = no neuropathy, 1 = mild neuropathy, 2 = moderate neuropathy, 3 = severe neuropathy) (24). Electrophysiological measurements were performed with surface electrodes, with the lower limbs maintained at 32°C and the upper limbs at 33°C. The test included an assessment of the peroneal and median motor nerves and sural, median, and ulnar sensory nerves.

Pain Rating Scores and Treatment Success

NRS score for pain during the day and night was the primary outcome measure of the study. SCS treatment success was defined as ≥50% pain relief on the basis

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of day and night NRS pain score for 4 days (27) or a PGIC score for pain and sleep of ≥6 on a 7-point Likert scale (1 = very much worse, 7 = very much improved) (28,29). A score of ≥6 on the PGIC indicates a clinically important difference. In addition, we report NRS score reductions of ≥30% because these relate to a clinically important difference in pain intensity as perceived by the patient (27,30, 31). Outcome measures were assessed at baseline, after 12 months, and each year thereafter until 5 years' follow-up. Furthermore, associations between baseline characteristics (i.e., duration of diabetes, duration of painful symptoms, MDNS, NRS score, type of diabetes, BMI, age, sex, HbA_{1c}) and SCS treatment success during trial stimulation were assessed.

Treatment Failure

For assessment of the sustainability of SCS treatment, failure was defined by ceasing to use the SCS system and ultimately the removal of the SCS device. Study entrance date and date of removal of the system were used to calculate the duration of SCS therapy in months. Furthermore, associations between baseline characteristics (i.e., duration of diabetes, duration of painful symptoms, MDNS, NRS score, type of diabetes, BMI, age, sex, HbA_{1c}) and long-term SCS treatment failure were assessed.

Complications

Complications and adverse events of SCS in PDPN were documented. Complications were defined as any event that required a patient visit (i.e., superficial or deep infections, pocket pain, painful or inadequate stimulation, battery or lead replacements or relocations, SCS reprogramming).

Statistical Analysis

Cross-sectional NRS and PGIC scores were used to calculate the percentage of patients experiencing treatment success. Baseline characteristics were described by using mean and SD or absolute value and percentage for continuous and categorical characteristics, respectively. Differences between baseline day and night NRS pain scores and NRS pain score at each consecutive year after baseline were analyzed by using a linear mixed-effects regression model with a random intercept to account for the repeated measures within each patient. Associations between baseline characteristics (i.e., duration of diabetes, duration of painful symptoms, MDNS, NRS score, type of diabetes, BMI, age, sex, HbA_{1c}) and SCS trial stimulation success were tested by means of logistic regression analysis. Kaplan-Meier survival analyses were used to evaluate the time to treatment failure (removal of the SCS system). Patients who enrolled in the study after February 2012 were followed for 4 years; hence, they were censored from analysis at 5 years' follow-up. The strength of association between baseline characteristics and treatment failure was evaluated with univariable Cox proportional hazards regression. All analyses were performed with SPSS version 23 statistical software (SPSS Corporation, Chicago, IL). $P \leq 0.05$ was considered statistically significant.

RESULTS

Patients

Between January 2009 and 28 February 2013, 137 patients with PDPN were screened at the MUMC+ and Radboud UMC. Forty-eight patients met the inclusion criteria and underwent trial stimulation. After trial stimulation, 40 of these 48 patients (83%) reported treatment success (i.e., ≥50% pain relief during the day or night or a score of ≥6 ["much improved" or "very much improved"] on the PGIC scale for pain and sleep) and received a permanent implant of the SCS device. During 5 years of follow-up, a maximum of four patients per time point did not return their questionnaires (two patients did not return their questionnaires at two time points). Seven patients were censored at 5 years because they did not complete the total follow-up at the time of the analyses (Supplementary Fig. 1). Patient baseline demographics and clinical characteristics are presented in Table 1.

Pain Rating Scores and Treatment Success

After 1-year follow-up, both day and night mean NRS pain scores decreased from 6.7 to 3.8 and 3.9, respectively ($P < 0.001$). After 5 years of follow-up, mean NRS scores during day and night were 4.3 and 4.6, respectively. Statistical analysis revealed that pain scores for each consecutive follow-up measurement were statistically significantly lower than the average baseline pain score. Average pain scores after implantation did not differ significantly from one another (Supplementary Fig. 2).

A pain reduction of ≥50% during the day was observed in 42% of patients (15 of 36) after 1 year of follow-up, 43% (15 of 35) after 2 years, 47% (16 of 34) after 3 years, 37% (11 of 30) after 4 years, and 36% (8 of 22) after 5 years. NRS pain score reductions of ≥50% during the night were observed in 36% of patients

Table 1—Baseline characteristics of all included patients, patients with a permanent implant, and patients with failed trial stimulation

Characteristic	All included patients (n = 48)	Patients with permanent implant (n = 40)	Patients with failed trial stimulation (n = 8)
Age	57.4 (9.9)	56.8 (9.5)	60.8 (11.7)
Sex			
Male	30 (62.5)	27 (67.5)	3 (37.5)
Female	18 (37.5)	13 (32.5)	5 (62.5)
Type 1 diabetes	5 (10.4)	5 (12.5)	0 (0)
Type 2 diabetes	43 (89.6)	35 (87.5)	8 (100)
Years of diabetes	13.3 (12.6)	14.2 (13.3)	8.9 (7.9)
Pain as a result of diabetes (years)	5.4 (4.3)	5.6 (4.4)	4.6 (3.5)
NRS baseline	6.5 (1.8)	6.7 (1.8)	5.6 (1.6)
HbA_{1c} (mmol/mol)	68.3 (25.7)	67.9 (25.3)	70.8 (32.2)
HbA_{1c} (%)	8.4 (2.3)	8.4 (2.3)	8.6 (2.9)
BMI (kg/m^2)	29.1 (4.1)	29.1 (4.1)	29 (4.1)
MDNS score			
0	5 (10.4)	5 (12.5)	0 (0)
1	12 (25)	10 (25)	2 (25)
2	20 (41.7)	16 (40)	4 (50)
3	11 (22.9)	9 (22.5)	2 (25)

Data are mean (SD) or n (%).

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(13 of 36) after 1 year of follow-up, 40% (14 of 35) after 2 years, 35% (12 of 34) after 3 years, 33% (10 of 30) after 4 years, and 32% (7 of 22) after 5 years. Reductions of ≥30% in NRS score during the day and night are presented in Table 2.

The percentage of patients reporting (very) much improvement on the PGIC scale for pain and sleep were 72% and 53% (26 and 19 of 36), respectively, after 1 year of follow-up, 54% and 37% (19 and 13 of 35) after 2 years, 53% and 29% (18 and 10 of 34) after 3 years, 53% and 47% (16 and 14 of 30) after 4 years, and 50% and 32% (11 and 7 of 22) after 5 years.

Treatment success was observed in 86% of patients (31 of 36) after 1 year of follow-up, 71% (25 of 35) after 2 years, 77% (26 of 34) after 3 years, 67% (20 of 30) after 4 years, and 55% (12 of 22) after 5 years (Table 2). After 4 years of follow-up, five of seven patients who were censored at 5 years experienced treatment success. Logistic regression revealed no associations between baseline characteristics and trial stimulation success.

Treatment Failure

The median follow-up duration of patients in our study was 60 months (minimum 1 month, maximum 60 months). Kaplan-Meier treatment survival analyses showed that 80% of patients with a permanent implant still used their SCS device after 5 years.

Univariate Cox proportional hazards regression revealed a higher MDNS to be associated with failure of treatment and subsequent removal of the SCS system (hazard ratio 3.9 [95% CI 1.3–11.6]; $P = 0.014$), whereas a higher baseline NRS pain score during the night was associated with a decreased risk of treatment failure and removal of the SCS system (0.8 [0.6–1.0]; $P = 0.045$) (Fig. 1).

Complications and Adverse Events

In one patient, an infection of the SCS system occurred 6 weeks after implantation, which led to removal of the system as previously described (11). A second patient presented with an infection of the SCS system 2 months after implantation. Despite adequate treatment, this patient developed a chronic pocket infection with *Staphylococcus aureus*, which led to removal of the SCS system 8 months after implantation. The remaining six device removals were the result of sustained lack of treatment success.

Nineteen patients who did not have their device removed and did not undergo battery replacements were still using the battery that was implanted at the start of the study. Eight patients underwent one battery replacement, and five underwent two battery replacements over a period of 5 years. Ten patients reported pain in the subcutaneous battery pocket during the 5 years of follow-up. In one patient, the battery caused considerable discomfort for a prolonged period. Twenty months after implantation of the device, the battery was relocated in a caudolateral direction. Nineteen months later, the patient reported recurrent discomfort caused by the battery, which was left in place during the 5-year period of the current study. Four leads were damaged and replaced during 5 years of follow-up, and another five leads were repositioned to optimize paresthesia coverage (Table 3).

Adjustments in the electrical programming are accountable for the majority of patient visits. Electrode configuration, pulse width, and frequency were adjusted multiple times in 23, 31, and 28 patients, respectively. Pulse width was increased and decreased in 29 and 36 of 65 patient visits, respectively. Frequency was increased and decreased in 32 and 18 of 50 patient visits, respectively.

Table 2—Day and night NRS pain scores

	Baseline	12 months	24 months	36 months	48 months	60 months
NRS day	6.7 (1.8)	3.8 (2.3)	4.1 (2.6)	3.8 (2.6)	4.2 (2.4)	4.3 (2.2)
NRS night	6.7 (2.2)	3.9 (2.4)	4.1 (2.8)	3.9 (2.7)	4.4 (2.4)	4.6 (2.5)
NRS ≥50% pain reduction during day	—	15 of 36 (42)	15 of 35 (43)	16 of 34 (47)	11 of 30 (37)	8 of 22 (36)
NRS ≥50% pain reduction during night	—	13 of 36 (36)	14 of 35 (40)	12 of 34 (35)	10 of 30 (33)	7 of 22 (32)
NRS ≥30% pain reduction during day	—	23 of 36 (64)	20 of 35 (57)	22 of 34 (65)	16 of 30 (53)	12 of 22 (55)
NRS ≥30% pain reduction during night	—	21 of 36 (58)	19 of 35 (54)	25 of 34 (74)	18 of 30 (60)	11 of 22 (50)
PGIC pain	—	26 of 36 (72)	19 of 35 (54)	18 of 34 (53)	16 of 30 (53)	11 of 22 (50)
PGIC sleep	—	19 of 36 (53)	13 of 35 (37)	10 of 34 (29)	14 of 30 (47)	7 of 22 (32)
Treatment success	—	31 of 36 (86)	25 of 35 (71)	26 of 34 (77)	20 of 30 (67)	12 of 22 (55)

Data are mean (SD) or *n* of *N* (%). Number of patients scoring (very) much improved on the PGIC scale. Treatment success is defined by a ≥50% decrease in day or night NRS pain score or a PGIC score of ≥6.

CONCLUSIONS

This prospective study indicates that SCS treatment results in decreased pain rating scores compared with baseline during 5 years of follow-up. Treatment success was achieved in 86% of patients at the 1-year follow-up assessment and in 55% of patients with PDPN after 5 years. Furthermore, this study demonstrates that MDNS is associated with treatment failure during 5 years of follow-up.

The success percentages observed in the current study are comparable to those reported in prospective studies on SCS in other neuropathic pain conditions like CRPS-1 and FBSS (14–16). The current data related to treatment success are based on only those patients who are still using their SCS device and thus, do not take into account those who underwent removal of the SCS system and were consequently lost to follow-up. Therefore, in addition to reporting primary outcome measures of patients with an implanted device at measurement time points, we report treatment failure (removal of the SCS device) over a 5-year period to evaluate the sustainability of SCS treatment in all patients who underwent a positive trial stimulation period. Furthermore, we evaluated associations between baseline characteristics and trial stimulation

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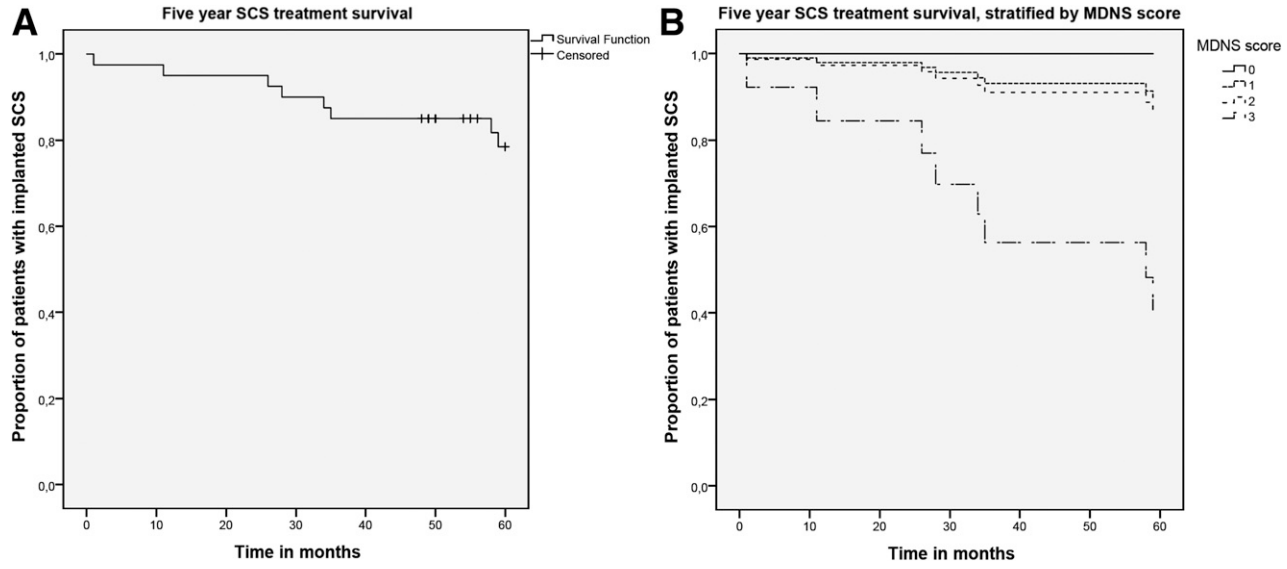

Figure 1—*A*: Failure curve of SCS implantation in patients with PDPN with positive trial stimulation. *B*: Failure curve of SCS implantation in patients with PDPN with positive trial stimulation stratified by MDNS score. Failure is defined as removal of the SCS system.

success or treatment failure during 5 years of follow-up.

Survival analysis showed that after 5 years, an estimated 80% of patients with PDPN with a permanent SCS implant were still using the device. The percentage of SCS treatment failure in this cohort was comparable to that reported in a prospective cohort study of patients with CRPS-1 after 5 years (14). On the basis of the current results, we conclude that the effectiveness of SCS sustained in patients with PDPN confirms previous observational results (26,32–35). Therefore, we believe that the financial costs associated with SCS in patients with PDPN should be evaluated with the perspective of longer-term treatment efficacy (i.e., at least 5 years). Recently, a randomized controlled study of the cost-effectiveness of SCS in patients with PDPN showed that the probability of SCS being cost-effective over a time horizon of 1 year ranges from 0 to 46%, with willingness to pay threshold values ranging between €20,000 and €80,000 per quality-adjusted life year (36). The authors extrapolated these data in patients with PDPN to 4 years on the basis of the estimated battery longevity at which point SCS treatment became cost-effective. Because SCS treatment success is maintained over at least 5 years in patients with PDPN and >50% of patients still use their initial SCS device after 5 years, SCS can be considered a cost-effective long-term treatment modality in patients with PDPN.

Although today SCS is established as a successful and widely applied technique to treat painful symptoms in various neuropathic pain disorders, a proportion of patients still do not respond to SCS or cease to benefit from SCS over time (13–15). Therefore, identification of predictive factors for successful trial stimulation or long-term treatment failure after implantation of a permanent SCS device is important. Psychosocial factors have previously been described to have predictive value for short-term SCS treatment success in candidates for SCS in general (37). To date, disease or patient-related demographic characteristics have not yet been reported as predictive factors for stimulation success or long-term treatment failure. In the current study population, no associations were observed between patient baseline characteristics and SCS trial stimulation success in patients with PDPN, which is in line with the literature evaluating patient-related factors and pain relief in other neuropathic pain disorders. A systematic review and meta-regression analysis of 74 studies, including 3,025 patients with chronic back or leg pain, showed no predictive patient-related factors of pain relief up to 24 months (18). However, we observed an association between baseline MDNS and SCS treatment failure (removal of the SCS device) during 5 years of follow-up in patients with PDPN, although only eight events occurred. MDNS is primarily based on nerve conduction studies combined with neurological examination of large-fiber sensory functioning (24). Therefore, the MDNS is considered indicative of the severity of the polyneuropathy. Patients with PDPN with an MDNS of 3 have a profound dysfunction of large sensory fibers (24). In

Table 3—Complications related to SCS treatment during 5-year follow-up

	Complications	Patients
Complication or adverse effect		
Deep infection	2	2 (5)
Superficial infection	0	0 (0)
Pocket pain	12	10 (25)
Uncomfortable stimulation	9	9 (23)
Equipment-related problem		
Battery relocation	1	1 (3)
Lead revision	5	4 (10)
Lead replacement	4	3 (8)
Battery replacement	18	13 (33)

Data are *n* or *n* (%).

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1996, SCS was shown to be ineffective in these patients with a severe loss of vibration and joint-position sense, which led to the hypothesis that the central nervous system plays a role in PDPN (10). Indeed, imaging studies have shown profound changes in both the brain and the spinal cord of patients with PDPN (38,39). The working mechanism of SCS is explained by activation of large myelinated sensory fibers in the dorsal column of the spinal cord (40). Dysfunction of these large myelinated sensory fibers, as likely to occur in patients with high MDNS, results in failure of SCS. Nonetheless, 40% of patients with PDPN with the highest MDNS still use their SCS device after 5 years. Therefore, patients with PDPN with a high MDNS should not be deprived of SCS treatment. However, the results can help to inform patients with PDPN who are seeking SCS treatment. The modest but significant association between lower NRS pain scores during the night and SCS treatment failure (removal of the SCS device) can be explained by the therapeutic window for SCS being smaller with a lower baseline pain score.

A limitation of the current study is the absence of a control group. Short-term treatment successes in patients with PDPN compared with a control group have previously been described (11,13). Patients in the control group were offered treatment after 6 months and then enrolled in the current prospective study. Furthermore, the total study population comprised two separate prospective cohorts of patients with PDPN with identical inclusion and exclusion criteria (11,26). Therefore, the study enrollment period was 4 years, which may have resulted in incremental expertise of surgeons and/or pain nurses who define the SCS settings. However, this reason is unlikely because only one complication (lead revision) occurred during follow-up of the first cohort and no significant differences in patient visits were noted. In general, the complication rate in this study cohort was low and in line with previous literature (12,14–17). Nonetheless, SCS should be considered only when other, less-invasive therapies have failed. Furthermore, the reported NRS and PGIC scores and success percentages are based on cross-sectional results and do not take into account missing or censored data. Therefore, we performed survival analyses to provide insight into the follow-up of all patients included at the start of follow-up. Everyone should be considered at risk for failure at the start of follow-up. Hence, only patients who had received a permanent implant were selected for this analysis. For assessment of the sustainability of SCS treatment, failure was defined by ceasing to use the SCS system and, ultimately, removal of the SCS device in those who received a permanent implant after the trial period. This analysis, therefore, is based on 40 patients with a permanently implanted SCS device and is not influenced by missing data. The patients who were censored (only after 4 years) have complete follow-up data until 4 years and are taken into account by the survival analysis. Therefore, the survival analysis adds value to the reported success percentages in this study, even after 4 years. Finally, changes in the use of pain medication could possibly influence the outcome of studies investigating the effect of SCS. Patients who enrolled in the current study did not benefit from pharmacological treatment and received SCS as a last-resort treatment modality. The results of pharmacotherapy alone in these patients have been described previously (11,13). In the current study, 9 patients reported an increased use of pain medication at their last assessment compared with baseline, whereas 10 reported less pain medication and 21 did not change their pain medication.

In conclusion, we demonstrate that SCS is successful in reducing pain symptoms in patients with PDPN with chronic neuropathic pain symptoms in the lower extremities up to 5 years after the start of SCS treatment. We also show that SCS is a sustainable treatment modality for 80% of these patients for at least 5 years. Moreover, we show that the severity of neuropathy (on the basis of a higher MDNS at baseline) is associated with a higher chance of long-term treatment failure (removal of the SCS device) during a follow-up of 5 years.

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