



Spinal Cord Stimulation and Pain Relief in Painful Diabetic Peripheral Neuropathy: A Prospective Two-Center Randomized Controlled Trial

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OBJECTIVE

Painful diabetic peripheral neuropathy (PDPN) is a common complication of diabetes mellitus. Unfortunately, pharmacological treatment is often partially effective or accompanied by unacceptable side effects, and new treatments are urgently needed. Small observational studies suggested that spinal cord stimulation (SCS) may have positive effects.

RESEARCH DESIGN AND METHODS

We performed a multicenter randomized clinical trial in 36 PDPN patients with severe lower limb pain not responding to conventional therapy. Twenty-two patients were randomly assigned to SCS in combination with the best medical treatment (BMT) (SCS group) and 14 to BMT only (BMT group). The SCS system was implanted only if trial stimulation was successful. Treatment success was defined as $\geq 50\%$ pain relief during daytime or nighttime or “(very) much improved” for pain and sleep on the patient global impression of change (PGIC) scale at 6 months.

RESULTS

Trial stimulation was successful in 77% of the SCS patients. Treatment success was observed in 59% of the SCS and in 7% of the BMT patients ($P < 0.01$). Pain relief during daytime and during nighttime was reported by 41 and 36% in the SCS group and 0 and 7% in the BMT group, respectively ($P < 0.05$). Pain and sleep were “(very) much improved” in 55 and 36% in the SCS group, whereas no changes were seen in the BMT group, respectively ($P < 0.001$ and $P < 0.05$). One SCS patient died because of a subdural hematoma.

CONCLUSIONS

Treatment success was shown in 59% of patients with PDPN who were treated with SCS over a 6-month period, although this treatment is not without risks.

Painful diabetic peripheral neuropathy (PDPN) is a common complication of diabetes mellitus (DM), and prevalence of PDPN ranges from 10 to 26% (1–3). In many patients, the pain is of such intensity that it has a major impact on patients’ health-related quality of life (HRQoL) and functional ability, including interference with general activity, mood, mobility, work, social relations, sleep, and enjoyment of life (4).

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A slide set summarizing this article is available online.

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Currently, PDPN can only be treated symptomatically; a variety of medications, alone and in combination, is often only partially effective or is accompanied by unacceptable side effects (5–7). Given the limited effectiveness of pharmacological treatment, alternative treatment strategies have been sought to alleviate pain, including spinal cord stimulation (SCS). In SCS, an electrode is positioned posterior in the epidural space to the dorsal column at the level of the nerve roots that transmit the nociceptive information from the painful area. The epidural lead is connected to a battery producing an electrical current, which induces paraesthesia, a sensation that suppresses the pain according to the Gate Control theory (8). Patients can reduce or increase the intensity of the electric current by means of a device that uses radio frequency transmission.

Several observational studies suggested that SCS may have a positive effect on pain in PDPN patients, with 23 out of 31 patients (74%) reporting a pain relieving effect of $\geq 50\%$ after 1 year of treatment (9–13). Three studies reported a sustained treatment effect (2–7 years) of SCS in PDPN patients (9,10,14). As SCS is a relatively expensive therapy (~12,000 Euros per patient) and not without risks, such as technical complications, there is a need for randomized controlled trials (RCTs) confirming its effectiveness in PDPN.

Therefore, we performed a multicenter RCT to determine whether SCS treatment in combination with best medical treatment (BMT) (SCS group) is more successful compared with BMT only (BMT group). Treatment success was defined as a $\geq 50\%$ pain relief in pain intensity during daytime or nighttime, or an improvement for pain and sleep of ≥ 6 in the score of the patient global impression of change (PGIC) scale.

RESEARCH DESIGN AND METHODS

Study Design

This study was designed as a prospective multicenter RCT to assess the effectiveness of SCS in combination with BMT (SCS group) compared with BMT only (BMT group) in patients with PDPN in the lower limbs on pain, HRQoL, and functional ability. Prior to inclusion, all patients were treated with BMT according to the international guidelines (5,7,15)

and the treatment algorithm of Jensen et al. (6). Invasive therapy, such as intrathecal drug delivery, was not allowed. A steering committee was responsible for the design of the study and for developing the protocol (available at ClinicalTrials.gov, NCT01162993). The study was performed at the outpatient pain clinics of the Maastricht University Medical Centre (MUMC⁺) and Radboud University Medical Center (Radboud UMC). The study was approved by the medical ethics committee of the MUMC⁺ and the institutional review board of the Radboud UMC. An independent data and safety monitoring board reviewed the study procedures and outcomes.

Patients

Patients with DM between 18 and 80 years of age, suffering from moderate to severe PDPN present in the lower limbs according to the Michigan Diabetic Neuropathy Score (MDNS) (16), were recruited from the outpatient pain clinics and the diabetic outpatient clinics of the two participating centers and were screened for eligibility. Inclusion criteria were as follows: insufficient pain relief and/or unacceptable side effects with drug treatment according to the guidelines and the algorithm described for PDPN by Jensen et al. (6), including antidepressants, antiepileptic drugs, opioids, or a combination of these therapies, pain present for >12 months, with a mean pain intensity during daytime or nighttime on a numeric rating scale (NRS) of 5 or higher, and, if necessary, a psychological assessment was performed.

Exclusion criteria were as follows: neuropathic pain most prevalent in the upper limbs (NRS >3); neuropathy or chronic pain of other origin than DM; recent neuromodulation therapy (<1 month before the intake-visit); drug, medication, or alcohol (>5 units/day) abuse; insufficient cooperation from the patient (little motivation, understanding, or communication); blood clotting disorder; immune deficiency; peripheral vascular disease with no palpable foot pulses at both feet (inclusion was possible if pulses were absent, but Doppler ankle-brachial index was between 0.7 and 1.2 in both feet); active foot ulceration; life expectancy <1 year; pacemaker; local infection or other skin disorders at site of incision; psychiatric problems potentially interfering with

cooperation in the study; pregnancy; severe cardiac or pulmonary failure ($>$ NYHA classification II); unstable blood glucose control (change in hemoglobin A_{1c} [HbA_{1c}] $>1.0\%$ in the 3 months preceding the trial); and use of oral anticoagulation that could not be stopped for a period of 10 days around the implantation procedure.

Randomization

Prior to randomization, all patients gave written informed consent. Patients were randomized between two groups by a computerized randomization. An independent data manager designed the randomization in a 3:2 ratio to the SCS group or BMT group, with stratification according to age, sex, type of DM, and severity of the PDPN according to the MDNS (16). This randomization ratio was chosen to facilitate the inclusion of participants. Treatment with SCS or BMT was only performed for 6 months. The surgical procedure for implantation of the SCS system was performed by four pain specialists (two at MUMC⁺ and two at Radboud UMC), all with extensive experience of >5 years.

Lead Placement, Trial Stimulation, and Criteria for Permanent SCS Implantation

Implantation of the SCS octapolar lead (Octad lead; Medtronic, Minneapolis, MN) was performed using local anesthesia and antibiotic prophylaxis. The patient was placed in prone position, and by using fluoroscopy, the epidural space was entered with a Tuohy needle at the lumbar level. Subsequently, the lead was advanced through the needle and connected to an external programmable stimulator (N'Vision; Medtronic). The position of the lead over the thoracic level and settings of the external stimulator were tailored for each patient in order to reach optimal paraesthesia coverage. Thereafter, the lead was anchored to the paraspinal fascia of the interspinous ligament and an extension lead was threaded through the skin, fixed, and connected to an external stimulator (External Neurostimulator Trialing System; Medtronic). After implantation, patients were admitted to the hospital for 24 h. Patients were discharged from the hospital if no change in position of the lead was seen after X-ray verification.

After a 2-week trial stimulation, the spinal cord stimulator (Synergy Versitrel or PrimeAdvanced; Medtronic) was implanted if the NRS for the intensity of pain during daytime or nighttime for the last 4 days of the trial period was at least 50% lower than the baseline score, or if there was a score of 6 or higher ("much improved" or "very much improved") on the PGIC scale for pain and sleep. After antibiotic prophylaxis, the spinal cord stimulator was placed just cranial to the greater gluteal muscle in a subcutaneous pocket or in the anterior abdominal wall and was connected by a tunneled new sterile extension lead to the stimulation lead, under local anesthesia. The first extension lead was removed. The patient remained in the hospital for 24 h while antibiotic prophylaxis was continued. If trial stimulation was unsuccessful, the stimulation lead was removed.

Outcome Measurements

Basic demographic data and PDPN history were obtained, including duration of DM, duration of painful symptoms, type of DM, length, weight, age, sex, and glycohemoglobin (HbA_{1c}).

Outcome measures were assessed at baseline and at 3 and 6 months for all patients; SCS patients received an extra assessment to evaluate the trial stimulation at 2 weeks.

Treatment success of SCS at 6 months was predefined in the protocol as follows: $\geq 50\%$ relief of pain intensity on an NRS for 4 days (17) during daytime or nighttime or a score of ≥ 6 on a 7-point Likert scale (1 = very much worse and 7 = very much improved) of the PGIC scale for pain and sleep (18,19). A score of 6 or higher on the PGIC indicates a clinically important difference.

In addition, we measured pain severity, pain interference with daily life, pain characteristics, HRQoL, pain interference with sleep, sleep quality and quantity, mood, and registered medication use at all time points.

The modified Brief Pain Inventory for Diabetic Peripheral Neuropathy was used to measure pain severity and pain interference in daily life, which were averaged to form two composite scores, the Pain Severity Index (PSI) and the Pain Interference Index (PII) (18).

Neuropathic pain qualities were measured using the Neuropathic Pain Scale,

which assesses two global and eight specific qualities of neuropathic pain (19).

HRQoL was measured with the EuroQol five dimensions (EQ-5D) (20). In this instrument, a utility score can be computed for each of five health states, based on preferences from a general population in the U.K., i.e., the U.K. tariff (21). Additionally, patients can rate their current health on a visual analog scale (22). In addition, the Medical Outcomes Study SF-36 (MOS SF-36) (23,24) was used to evaluate patients' perceived health state, which is composed of 36 questions and standardized response choices, organized into eight multi-item scales that can be averaged to form two composite scores, the physical component score (PCS) and the mental component score (MCS).

The impact of PDPN on sleep quality and quantity was assessed using the Medical Outcomes Study Sleep Scale. A nine-item Sleep Problems Index was calculated, and quantity of sleep was scored as the average hours of sleep per night reported over the past week. Sleep was scored as optimal in cases of 7–8 h of sleep per night (25,26).

Mood was assessed with the Beck Depression Inventory (BDI), a self-report inventory for measuring the severity of depression (27). Finally, we documented complications and (serious) adverse events of SCS.

Medication use was registered and was scored in terms of increased, reduced, no change in medication use, switched to other medication, or completely stopped with medication.

Statistical Analysis

Data from prospective pilot studies were used to estimate the required sample size (10–12,28). The prespecified definition of clinically relevant pain relief was a reduction of 50% on the NRS and/or improvement on the PGIC for pain and sleep. We calculated that a sample of 40 patients with PDPN was required in order to detect a difference in success of 40% between SCS and BMT compared with BMT. We assumed a proportion of success in the SCS group of 50% and in the BMT group of 10%, with a power of 80% and a two-sided type I error of 0.05, allowing for 10% lost to follow-up.

The statistical analysis was carried out according to the intent-to-treat (ITT) principle, which included all patients who were

randomized, even those patients without a postbaseline measurement. Dropouts were classified as failures for SCS. The efficacy analysis was a logistic regression of the difference between the SCS group and the BMT group in the proportion of patients with a success of treatment over the course of 6 months. For the PGIC score (dichotomized as a score of < 6 or ≥ 6), there was no pretreatment data and therefore only differences between the two groups were calculated. We performed a multivariate logistic regression to adjust for the effect of possible unbalanced distributions of the baseline characteristics (age, sex, and MDNS score) on the primary outcome measure.

Linear mixed model analysis was performed to analyze the differences in trends of the outcome measures. A random intercept regression model examined the differences in linear rate of change between the SCS group and the BMT group over the course of 6 months. This model measured each patient's deviation from the population average change over time and included a random intercept for each subject. For this model, all available data (baseline and 3 and 6 months) were used. The model estimated fixed effects for treatment. All statistical analyses were performed using SPSS Statistics for Windows, version 20.0.

RESULTS

Patients

Between 1 February 2010 and 28 February 2013, we screened 110 patients with PDPN at the MUMC⁺ and at the Radboud UMC. Study enrollment, randomization, and follow-up are shown in Fig. 1. Patient baseline demographics and clinical characteristics are presented in Table 1.

In one patient, the implantation of the stimulation lead was complicated by a dural puncture, and the procedure of this patient was immediately stopped (see below). Therefore, 21 of the 22 patients who were assigned to the SCS group underwent a 2-week trial stimulation period. One patient was not willing to fill out questionnaires after negative trial stimulation. After 6 weeks, another patient withdrew from the study due to infection and removal of the SCS system.

Results of Trial Stimulation

Trial stimulation was successful in 17 of the 22 SCS group patients (77%). All 17

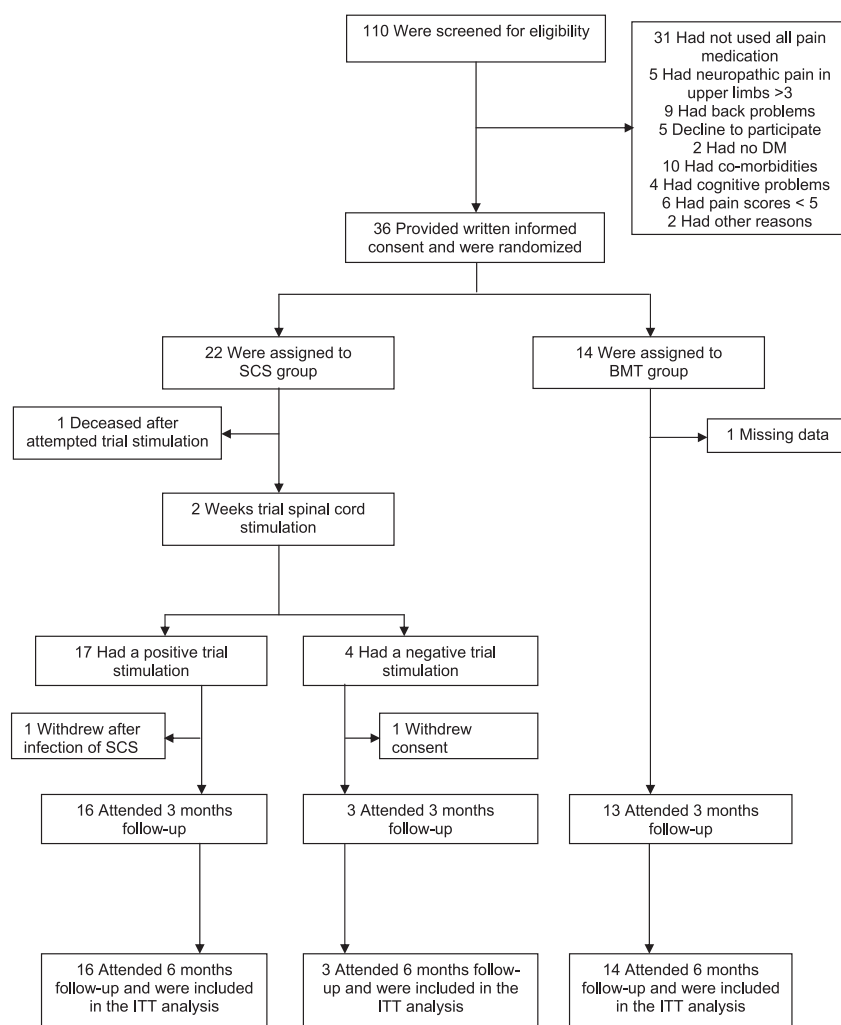


Figure 1—Randomization and follow-up.

patients reported pain relief during daytime of at least 50% as compared with baseline, and 12 patients (55%) showed reduced pain of $\geq 50\%$ during nighttime. All 17 patients had a minimal score of 6 (much improved) for the PGIC for pain and 14 patients (64%) for the PGIC for sleep.

Outcome Measurements

ITT analysis was performed for 22 patients assigned to the SCS group and 14 patients assigned to the BMT group. Outcome data were available for 19 patients (86.4%) in the SCS group and 14 patients in the BMT group (100%) at 6 months.

Treatment success of SCS was observed in 13 out of 22 patients (59%) and in 1 out of 14 BMT patients (7%) ($P < 0.009$) (Table 2). The mean pain score on the NRS during daytime in the

SCS group was reduced by 3.1 points at 6 months as compared with no change in pain score in the BMT group ($P < 0.001$) (Fig. 2). In total, nine patients (41%) reported $\geq 50\%$ pain relief during daytime in the SCS group, as compared with 0% in the BMT group ($P < 0.001$). Mean pain at night was reduced by 2.4 points in the SCS group compared with 0.9 points on the NRS in the BMT group ($P < 0.003$) (Fig. 2). Eight patients (36%) showed $\geq 50\%$ pain relief during nighttime in the SCS group, as compared with one patient (7%) in the BMT group ($P < 0.01$). Of the 22 SCS patients, 12 (55%) scored ≥ 6 (much improved) on the PGIC for pain ($P < 0.001$) and 8 (36%) scored ≥ 6 on the PGIC scale for sleep ($P < 0.011$). None of the BMT patients showed any difference on the PGIC scale for pain or sleep. After adjusting for possible unbalanced distributions of the

baseline characteristics, the OR for treatment success was 18.8 (95% CI 2.1–170.2). Sex was the only covariate that had a significant influence on the outcome, and adjusting for sex increased the OR to 24.7 (2.4–250.2). The results at 3 months were similar to the results obtained at 6 months and are presented in Supplementary Table 1.

Results of pain severity, pain interference with daily life, qualities of pain, HRQoL, pain interference with sleep quality and quantity, and mood in both groups are presented in Table 2 and Supplementary Table 1. Both the PSI and PII showed significant differences between the SCS and the BMT group ($P < 0.001$ and $P < 0.008$, respectively). The characteristics of neuropathic pain were improved in the SCS group compared with the BMT group, with the exception of deep pain. After 6 months, the mean utility score of the EQ-5D was increased in the SCS group with 0.25, and in the BMT group, the change was 0.00; this difference was not statistically significant ($P < 0.776$). No significant differences between the SCS and BMT groups were seen on the visual analog scale (VAS) of the EQ-5D (Fig. 3) and the MCS and PCS of the MOS SF-36. Mood, as assessed with the BDI, did not differ between the two groups. Sleep quantity, optimal sleep, and sleep quality were of relative poor quality in both groups, but no significant effect of SCS was observed (Table 2).

Seven out of 22 patients (32%) of the SCS group were able to reduce their pain medication, and for 2 of them, the SCS became the sole treatment for their PDPN pain. Twelve patients (55%) did not change their medication in combination with SCS treatment. Four patients (29%) in the BMT group reported an increased use of medication compared with baseline, and one patient changed to another category of neuropathic pain medication. In 9 out of 14 (64%) patients, medication use was unchanged as compared with baseline.

Complications and (Serious) Adverse Events

Serious adverse events were noted in two patients. Implantation of the lead for test stimulation was complicated by a dural puncture, causing a postdural puncture headache in one patient

Table 1—Baseline demographics and clinical characteristics of the study population

Characteristic	SCS group (N = 22)	BMT group (N = 14)
Age (years)	57.1 ± 12.4	56.5 ± 8.0
Male sex (n [%])	15 (68)	9 (64)
Type of DM		
Type 1 diabetes (n [%])	3 (14)	1 (7)
Type 2 diabetes (n [%])	19 (86)	13 (93)
Years of DM (years)	12.7 ± 10.1	12.6 ± 7.2
Years of pain due to DM (years)	6.0 ± 5.1	4.9 ± 3.6
HbA _{1c} (mmol/mol)†	66.9 ± 22.1	68.6 ± 29.4
HbA _{1c} (%)†	8.3 ± 2.0	8.4 ± 2.7
BMI‡	29.0 ± 4.3	30.3 ± 5.4
MDNS score§		
MDNS score 0	3	3
MDNS score 1	4	3
MDNS score 2	9	5
MDNS score 3	6	3

Plus-minus values are means ± SD. †HbA_{1c} is presented in mmol/mol and %. ‡BMI is the weight in kilograms divided by the square of the height in meters. §MDNS consists of a standard neurological examination, including vibration sense, light touch, pin-prick, tendon reflexes, and muscle strength, and standard nerve conduction study of two motor nerves (peroneal and median) and three sensory nerves (sural, median, and ulnar) performed on the nondominant site. Classes are defined as 0 = no neuropathy, 1 = mild neuropathy, 2 = moderate neuropathy, and 3 = severe neuropathy.

(male, 65 years of age). After conservative treatment was started, the patient was discharged from the hospital. Three days after the procedure, the headache suddenly increased and within minutes, the patient became unresponsive. The patient was transferred to the nearest hospital where a CT scan showed a large subdural hematoma over the left hemisphere with a diameter of 26 mm, causing a midline shift of 19.8 mm. Despite immediate surgical evacuation of the subdural hematoma, the patient did not regain consciousness and died 10 days after surgery.

Another patient contracted an infection of the SCS system 6 weeks after the SCS system implantation, which was subsequently removed. Despite treatment with antibiotics, the patient recovered slowly but not completely. The patient also developed an autonomic neuropathy. After a consultation with the patient, it was decided that the SCS system would not be reimplanted.

CONCLUSIONS

This prospective multicenter RCT involving patients with moderate to severe PDPN in the lower limbs showed that after 6 months, SCS treatment reduces pain more effectively compared with BMT only. SCS reduced both daytime

and nighttime pain. No differences were observed in HRQoL after SCS treatment. Finally, SCS treatment was not without any risk as two serious adverse events, which were both treatment related, occurred. Significant pain relief during daytime was shown in 41%, as compared with 55–60% in previous pilot studies, at 6 months (10–12). Furthermore, 55% of the SCS group showed a clinically important difference on the PGIC score for pain. The larger number of patients with an effect on PCIC can be explained by the fact that an increase of ≥6 score on the PGIC scale is associated with 30% pain reduction on the NRS scale and is experienced as clinically relevant (17,29,30). In this study, 11 out of 22 patients (50%) reported ≥30% pain relief on the NRS during daytime. During nighttime, ≥50% pain relief was noted in 36%, which was accompanied by a nonsignificant 1-h increase in sleeping time in the SCS patients. No differences were observed in HRQoL after SCS treatment.

As expected, our patients showed a poor HRQoL, and the participants reported utility scores of 0.25 (SCS group) and 0.33 (BMT group) at baseline, which were substantially lower compared with other studies that reported higher utility scores in PDPN patients (with a mean

0.61 [95% CI 0.56–0.66]) (31,32). In the SCS patients, the utility score improved from 0.25 to 0.50, which was mainly due to improvements on three dimensions of the EQ-5D: daily activities, pain, and mood. As pain and mood both have a relatively large weight in the regression-based calculation of the utility score, they largely accounted for the observed major improvement in the SCS group. Nevertheless, probably due to the large variability in the data, the differences between the SCS and BMT patients were not significantly different. Remarkably, patients' valuation of their current health state on the VAS of the EQ-5D showed no differences between the two groups. Patients in the SCS group showed hardly any improvements, despite reported pain relief and improved functioning in daily activities and mood at 6 months as compared with baseline. The difference between the general population (i.e., the utility scores) and patients' valuations (i.e., the VAS) has been explained by the adaptation phenomenon (33). Where PDPN patients are likely to adapt to changes in their health state, healthy individuals usually do not anticipate adaptation effects and thus value those health states differently (33,34). Another explanation for the discrepancy between the utility scores and VAS in PDPN patients is that they may have included dimensions in the valuation of their current health state other than those included in the descriptive system of the EQ-5D and subsequently weighted them differently (35). This also explains the nonsignificant change in MCS and PCS of the MOS SF-36. As discussed below, the number of participants in this RCT was limited; therefore studies with a larger number of participants are necessary to determine the effects of SCS on HRQoL.

Success of SCS seems highly dependent on the use of strict selection criteria and the use of a 2-week trial stimulation with predefined criteria to evaluate the efficacy of the trial stimulation. We used strict selection criteria (36) to include patients, including an NRS pain intensity ≥5 measured on an NRS at the lower extremities for at least 6 months, treated with best medical therapy and patients with a clear history of PDPN. Causes other than diabetic peripheral neuropathy were excluded, and if necessary, a psychological

Table 2—Outcomes in the SCS group compared with BMT group at 6 months, ITT analysis

Outcomes	Baseline		6 months	
	SCS group (N = 22)	BMT group (N = 14)	SCS group (N = 19)	BMT group (N = 14)
HbA _{1c} (mmol/mol) [†]	66.9 ± 22.1	68.6 ± 29.4	64.2 ± 15.1	72.1 ± 25.2
HbA _{1c} (%) [†]	8.3 ± 2.0	8.4 ± 2.7	10.9 ± 8.0	8.8 ± 2.3
NRS ≥50% pain reduction day (n/total n [%])			9/22 (41)	0/14 (0)***
NRS ≥50% pain reduction night (n/total n [%])			8/22 (36)	1/14 (7)**
PGIC for pain (n/total n [%])			12/22 (55)	0/14 (0)***
PGIC for sleep (n/total n [%])			8/22 (36)	0/14 (0)*
Treatment success (n/total n [%])			13/22 (59)	1/14 (7)**
mBPI-DPN [†]				
PSI	7.1 ± 1.5	6.3 ± 1.8	4.0 ± 2.8	6.5 ± 2.1***
PII	6.0 ± 1.9	5.3 ± 2.0	3.5 ± 2.6	5.5 ± 1.5**
NPS [‡]				
Deep pain	8.2 ± 1.5	7.6 ± 1.5	6.3 ± 2.9	7.4 ± 1.8
Surface pain	6.0 ± 3.3	6.5 ± 2.4	3.6 ± 3.4	6.4 ± 2.1**
Intensity	8.0 ± 1.5	7.6 ± 1.5	4.3 ± 3.0	7.3 ± 2.0***
Unpleasantness	7.9 ± 1.8	7.6 ± 1.7	5.4 ± 2.8	7.5 ± 1.6**
Coldness	4.2 ± 3.6	4.9 ± 4.0	2.2 ± 2.7	5.6 ± 3.1*
Hotness	6.9 ± 2.7	6.7 ± 3.5	2.9 ± 3.3	6.3 ± 2.5**
Dullness	7.6 ± 2.1	7.7 ± 2.4	4.6 ± 3.5	7.6 ± 1.7***
Sharpness	7.9 ± 1.9	7.3 ± 2.4	5.0 ± 3.3	7.7 ± 1.7**
Sensitivity	7.6 ± 2.5	6.5 ± 2.4	5.0 ± 3.4	7.1 ± 2.2*
Itching	3.9 ± 3.1	3.6 ± 3.3	1.6 ± 2.6	4.2 ± 3.2*
EQ-5D [§]				
Utility scores	0.25 ± 0.31	0.33 ± 0.32	0.50 ± 0.33	0.33 ± 0.29
Current health	53.9 ± 18.5	54.6 ± 16.7	57.6 ± 24.3	56.5 ± 14.2
MOS SF-36				
MCS	44.7 ± 13.5	45.3 ± 11.8	49.3 ± 11.5	46.7 ± 12.0
PCS	27.9 ± 7.5	31.7 ± 7.9	32.3 ± 10.5	30.5 ± 7.4
MOS-SS [¶]				
SPI-9	56.1 ± 15.6	53.0 ± 17.2	40.3 ± 19.6	52.9 ± 16.5
Quantity of sleep (h)	5.1 ± 1.9	6.1 ± 2.4	6.6 ± 1.8	5.4 ± 2.4
Optimal sleep (n [%])	6 (27)	0 (0)	5/22 (23)	3/14 (21)
BDI [#]	13.2 ± 7.3	13.7 ± 6.4	13.0 ± 9.8	14.4 ± 6.3

Plus-minus values are means ± SD. [†]The modified Brief Pain Inventory- Diabetic Peripheral Neuropathy (mBPI-DPN) assesses the severity of pain and its impact on daily functioning and forms two composite scores: the PSI and the PII. Zero means “no pain” or “does not interfere” and 10 “pain as bad as you can imagine” or “completely interferes.” [‡]The Neuropathic Pain Scale (NPS) includes two items that assess the global dimensions of pain intensity and unpleasantness and eight items that assess the specific qualities of neuropathic pain, in which 0 is “no pain or not” and 10 is “the most sensation imaginable.” [§]EQ-5D is a health status measure with respect to mobility, self-care, usual activities, pain or discomfort, and anxiety or depression (no problems, some problems, and extreme problems). A utility score of 1 represents “perfect health,” 0 represents “death,” and <0 “worse than death.” Self-rated current health status was assessed using a vertical, visual analog scale on which 0 indicates worst possible health and 100 indicates perfect health. ^{||}MOS SF-36 measures PCS and MCS and is converted to a 0–100 scale, with higher scores indicating higher levels of functioning or well-being. [¶]The Medical Outcomes Study Sleep Scale (MOS-SS) measures sleep quality and quantity. Sleep Problems summary 9 (SPI-9) scores range from 0 to 100 and higher scores indicate worse outcomes. [#]Severity of depression was measured by the BDI, and higher total scores indicate more severe depressive symptoms. **P* < 0.05 for the between-group difference in the ITT analysis. ***P* < 0.01 for the between-group difference in the ITT analysis. ****P* < 0.001 for the between-group difference in the ITT analysis.

assessment prior to inclusion was performed. A 2-week trial stimulation with predefined criteria was used to evaluate the efficacy of SCS. A negative trial stimulation was noted in 23% of the SCS patients, which is in line with previously published studies (10–12). These patients reported <10% pain relief during daytime and nighttime, as well as no change on the PGIC scale. As summarized by Tesfaye et al. (37), several anatomical or pathophysiological changes, including

both peripheral and central mechanisms, have been implicated in the development of pain in diabetic peripheral neuropathy. A possible explanation for the substantial number of negative trial stimulations might be the presence of permanent central changes in the spinal cord. Three observational studies reported a smaller mean spinal cord area index at the cervical and thoracic level in patients with diabetic peripheral neuropathy as compared with control patients without

DM (38–40). Whether involvement of the spinal cord is a primary or secondary event in diabetic peripheral neuropathy is not yet clear (39). In cases of spinal cord atrophy, we would expect differences in various neurological tests between patients with a positive and those with a negative trial stimulation. However, no differences in muscle strength, reflexes (knee and achilles tendon reflex), vibration sense, and joint position in the lower extremities were found. Thus, our data

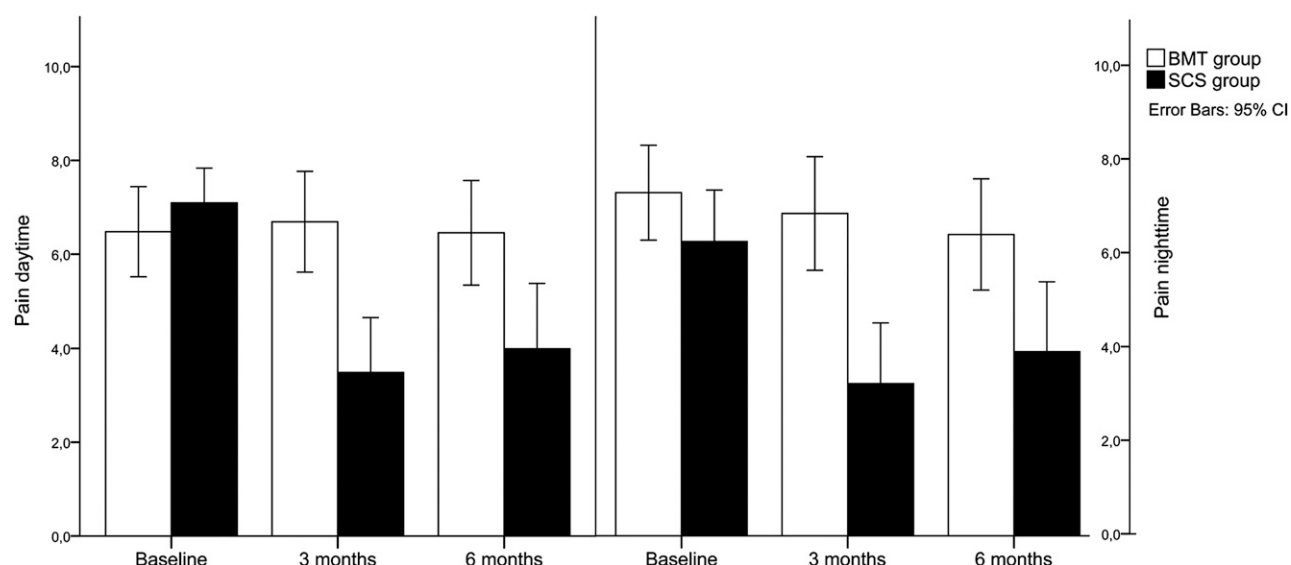


Figure 2—Mean pain scores at daytime and nighttime. ITT analysis.

indicate that given the number of negative trial stimulations, a trial stimulation should always be performed when SCS is considered.

Although SCS is effective in most patients, the treatment is not without risks. Review studies report SCS to be a safe intervention in neuropathic pain patients (41,42). The most common complications related to SCS are hardware related (lead migration, lead fracturing, connection failure, and discomfort), infection, subcutaneous hematomas, and cerebrospinal fluid leak (41–43). In our study, severe complications were noted in two patients (9%) during a period of 6 months

following implantation. In one patient, an infection occurred 6 weeks after SCS system implantation, and the patient responded to antibiotic management and removal of the SCS system. In the second patient, however, a dural puncture during the trial phase resulted in postdural puncture headache and subsequent development of a subdural hematoma with lethal outcome. To the best of our knowledge, a subdural hematoma is an extremely rare complication of SCS. After extensive review of the literature, we found one case report of a subdural hematoma after an SCS implant, where the patient suffered from minor head injury within 24 h

before dural tearing and showed full neurological recovery after emergent craniotomy (44). Although extensive examination of our patient's record was performed, no predictors for this devastating serious adverse event could be found. Except for this lethal complication, the complication rate in this study is comparable to that reported in literature (41–43). Nevertheless, given the invasive nature of SCS, our data underscore that SCS reduced pain but should be applied as a last resort treatment and only should be carried out in specialized centers by a specialist with excellent experience in performing SCS treatment.

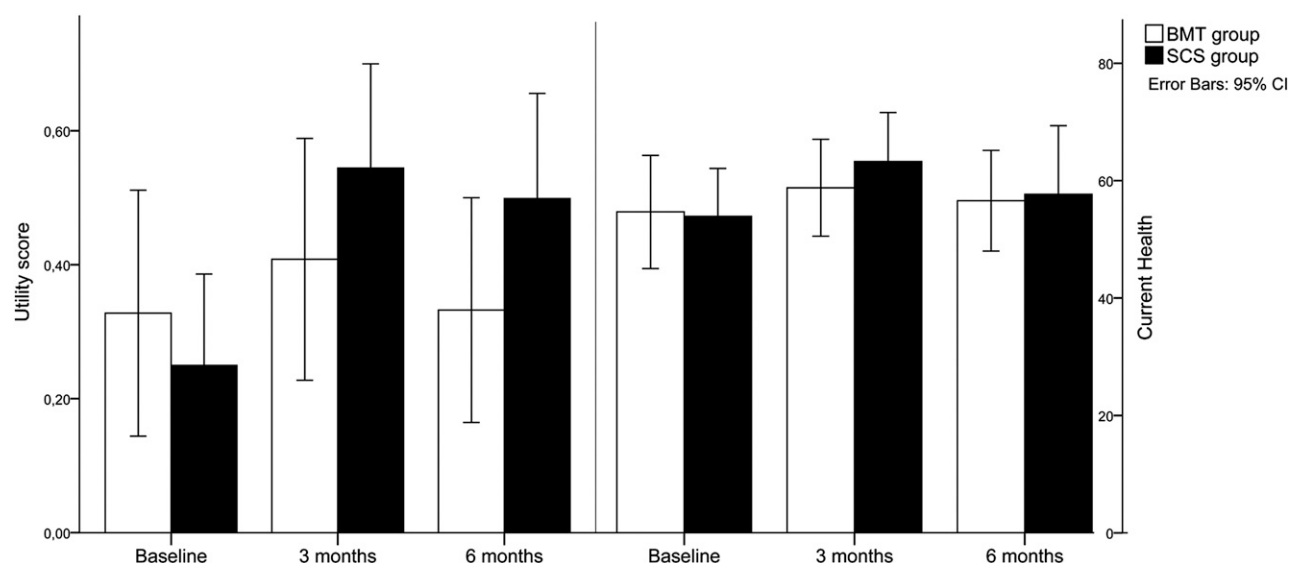


Figure 3—EQ-5D utility score and EQ-5D current health.

Our study has some limitations that need to be discussed. Patients with failure of pharmacological treatment and with high pain levels were screened and included. Therefore, the results cannot be generalized to patients with less pain. Some of the screened patients were referred to our clinic because of failure of previous treatment. Although some of the referring centers used a somewhat different treatment algorithm, all patients had been treated with pharmacological treatment as described in the current guidelines, including antidepressants, anti-convulsants, and/or opioids. As pain severity is not always related to the extent of neurologic abnormalities on clinical examination, the MDNS score was evenly distributed in our patients, leading to the possibility of referral of more severely affected patients. A major limitation of the study, like all studies using conventional SCS, was the fact that this study was not blinded, since paraesthesia accompanies SCS. Moreover, it is unethical and too invasive to implant a SCS system that is subsequently not used. Finally, PDPN is a progressive disease in which symptoms will be present in not only the feet and legs but will gradually progress proximally toward the hands and arms. We excluded patients with pain in the upper extremities as only the lower extremities were stimulated. Hence, it remains to be determined if SCS at both cervical and thoracic/lumbar spinal levels will be effective.

These limitations notwithstanding and including the risks, our findings show that in PDPN patients, SCS in combination with BMT results in clinically relevant pain relief over a 6-month period.

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