Pain relief and quality-of-life improvement after spinal cord stimulation in painful diabetic polyneuropathy: a pilot study†

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Editor’s key points

- Painful diabetic neuropathy is often difficult to manage with current pharmacological therapies.
- There is a limited understanding of which patients are most likely to respond to spinal cord stimulation (SCS).
- This exploratory study carefully characterizes pre-treatment pain and the effects of SCS.
- Further work is needed to develop understanding of who is most likely to respond to SCS.

Background. Painful diabetic polyneuropathy (PDP) is associated with high pain scores and is difficult to treat. Therefore, spinal cord stimulation (SCS) has been suggested as second-line treatment. In this study, the feasibility and efficacy of SCS in PDP were investigated, as well as the predictive value of clinical sensory testing for the treatment outcome.

Methods. Fifteen patients with intractable PDP in the lower limbs were recruited. During lead implantation, the feasibility of achieving adequate paraesthesia coverage using one stimulation lead was investigated. If trial stimulation was successful, a definitive neurostimulator was implanted. Pain intensity was scored using an 11-point numeric rating scale and patients’ global impression of change scale. Additionally, neuropathic pain characteristics, quality of life, sleep quality and mood were assessed. The predictive value of clinical sensory testing for the treatment outcome was analysed.

Results. Adequate paraesthesia coverage was achieved in 14 out of 15 patients. Clinically relevant pain relief was present in 11 patients after trial stimulation and 10 patients at 12 months. The quality of life was significantly increased at 2 weeks and 3 months in patients with successful SCS treatment. Several neuropathic pain characteristics and quality of sleep were improved at 2 weeks and 12 months. Preoperative clinical sensory testing did not differentiate between treatment responders from non-responders.

Conclusions. SCS seems to be an efficacious and feasible treatment for intractable PDP. In this exploratory study, it was not possible to predict the treatment outcome using clinical sensory testing. These results justify performing a randomized clinical trial.

Keywords: diabetic neuropathies; electric stimulation therapy; pain management; spinal cord; treatment outcome

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Painful diabetic polyneuropathy (PDP) is a common complication of diabetes mellitus (DM), affecting up to 25% of patients.1–4 Moderate-to-severe pain is present in 75% of the patients and frequently accompanied by other chronic medical conditions, e.g. depression, anxiety, and sleep disorders,5 often leading to increase in the health resource usage, diminished work ability, and decrement in quality-of-life expectations.

Pharmacological treatment of PDP is partially effective in one-third of patients and side-effects frequently occur, leaving many patients with inadequate pain relief.6 Therefore, spinal cord stimulation (SCS) has been suggested as second-line therapy in patients with intractable PDP. Two small-scale observational studies showed a pain-relieving effect of SCS in intractable PDP.7–9 However, the primary outcome parameters in these studies were limited to pain intensity, whereas the effects of SCS on quality of life, sleep, and depression were not systematically investigated.

Since SCS is an invasive and expensive treatment modality, selection of appropriate patients and prediction of SCS treatment outcome is important. In the previous publications, description of patient characteristics was limited to patient characteristic data, duration of DM and PDP and measurement of vibration perception thresholds.7–9

†This article is accompanied by Editorial 1.
The objectives of the present pilot study were two-fold. The first aim was to systematically investigate, in a well-described population of patients with intractable PDP, the impact of SCS on pain, various characteristics of neuropathic pain, mood, sleep, patients’ daily life, and quality of life. The second aim was to investigate the possibility of predicting the SCS outcome using preoperative clinical sensory testing.

Methods

The study was designed as a prospective open-label cohort study and the protocol was approved by the local Medical Ethics Committee (ref. 0-82-118) and CCMO (ref. NL246 28.068.08) and registered with Clinical Trials (ref. NCT00 802022). Patients were recruited through advertisement in a national diabetes journal. After informed consent, patients were included in the study and baseline measurements were performed. After implantation of the SCS lead, a 2-week trial period was performed. If trial stimulation was successful, a pulse generator was implanted and the follow-up measurements were performed at 3, 6, and 12 months in these patients. If the trial stimulation was unsuccessful, a follow-up measurement was performed at 12 months.

Patient selection

Fifteen patients (Table 1), with PDP (based on typical clinical pain description10 and excluding other possible causes) with neuropathic pain in the lower limbs, were screened for eligibility according to the Michigan Diabetic Neuropathy Score (MDNS) using clinical neurological examination followed by nerve conduction measurements. Inclusion criteria were: (i) duration of pain ≥12 months; (ii) previous unsuccessful drug treatments [including tricyclic antidepressants, alpha-2-delta agonist (pregabalin or gabapentin), dual serotonin and noradrenaline receptor inhibitor]; (iii) on average pain intensity during day or night of ≥5 on a numeric rating scale (NRS, ranging from 0 to 10); (iv) age between 18 and 75 years.

Exclusion criteria were: recent neuromodulation therapy; neuropathic pain predominantly present in upper limbs; neuropathy or chronic pain of other origin than PDP; use of opioids or abuse of drugs or alcohol; blood clotting disorders; known immune deficiency; peripheral vascular disease characterized by absent palpable peripheral pulses and/or ankle brachial index <0.7 at both feet; active foot ulceration; presence of a pacemaker; severe cardiac or pulmonary disease (NYHA ≥II); unstable blood glucose control (HbA1c variation ≥1% over 3 month period).

Implantation of the SCS system

Using local anaesthesia and antibiotic prophylaxis (cefuroxime/erythromycin), an octapolar SCS lead (Octad®, Medtronic, Minneapolis, MN, USA) was implanted percutaneously. After determination of the entry level in the epidural space (usually L4-L5), the SCS lead was inserted using fluoroscopy. Trial stimulation was then performed using a snaplid® connector and an external programmable stimulator (N’Vision®, Medtronic). After optimal paraesthesia coverage was achieved, the lead was anchored to the paraspinal fascia of the interspinous ligament and an extension wire was threaded through the skin and fixed.

The pain-relieving effect of SCS was evaluated during a 2-week trial stimulation period. If successful, a definitive pulse generator was implanted (see Methods section for the definition of ‘successful stimulation’). If trial stimulation was unsuccessful, the SCS lead was removed and the treatment as usual, i.e. pharmacological treatment,6 was continued. After antibiotic prophylaxis implantation of the pulse generator (Synergy Versitrel®, Medtronic, Minneapolis, MN, USA) was performed with the patient placed in lateral position under local anaesthesia. In all patients, the stimulator was placed just cranial to the greater gluteal muscle in a subcutaneous pocket. Using the SCS lead extensions, the connection with the electrode was made and, after checking the impedance, the wounds were closed.

Outcome measures

Pain relief was defined as the primary outcome in this feasibility study. The rationale for choosing the after outcome measures was primarily based on the recommendations given by the IMMPACT study group.11 All patients were assessed at baseline, 2 weeks, and 12 months. Patients who received a definite SCS were also measured at 3 and 6 months.

Pain relief

The primary outcome measure was pain intensity which was evaluated using a NRS-based pain dairy.12 The averages were calculated from the daily pain scores (3 times daily for 4 days) and nocturnal pain scores (once daily for 4 days). Peak pain intensity was also scored on a NRS. Additionally, change of painful symptoms compared with the baseline was assessed using the patients’ 7-point global

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristics and baseline characteristics. N, number; SD, standard deviation; DM, diabetes mellitus; BMI, body mass index; MDNS, Michigan Diabetic Neuropathy Score; md-ISS, modified INCAT sensory sum score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient characteristics</td>
<td>Gender, N (male/female) 8/7</td>
</tr>
<tr>
<td>Baseline characteristics</td>
<td>Age (yr) (range) 59.9 (50–72)</td>
</tr>
<tr>
<td></td>
<td>Duration DM (yr) 15.0 (18.4)</td>
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<tr>
<td></td>
<td>Duration neuropathy (yr) 10.0 (13.3)</td>
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<tr>
<td></td>
<td>Duration painful symptoms (yr) 4.9 (3)</td>
</tr>
<tr>
<td></td>
<td>BMI (kg m⁻²) 28.8 (3.2)</td>
</tr>
<tr>
<td></td>
<td>MDNS No neuropathy 0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Mild neuropathy 6 (40%)</td>
</tr>
<tr>
<td></td>
<td>Moderate neuropathy 7 (47%)</td>
</tr>
<tr>
<td></td>
<td>Severe neuropathy 2 (13%)</td>
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<td>md-ISS 6.8 (5.0)</td>
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</table>
impression of change (PGIC) Likert scale. ‘Completely resolved’ and ‘much improved’ were considered relevant improvement, whereas ‘worse than ever’ and ‘much worse’ were considered relevant worsening.

Clinically relevant pain reduction (pain daytime, pain night, or peak pain) was defined as ≥50% decrease of pain intensity. Success of SCS treatment was defined as clinically relevant pain relief on pain daytime and/or pain night and/or peak pain and/or PGIC for pain.

**Paraesthesia coverage**
An estimate of percentage of paraesthesia coverage of the painful area was made by the anaesthesiologist while performing the lead implantation. The criterion for adequate paraesthesia coverage was defined as ≥80% coverage of the painful area with one octalead. Paraesthesia coverage was scored on a dichotomous scale (i.e. either adequate or inadequate).

**Quality of life**
Health-related quality of life was assessed using the EuroQol 5 dimensions questionnaire (EQ-5D). From the EQ-5D, a utility score was calculated using a regression equation. Additionally, the Short Form-36 (SF-36) health status questionnaire was used to calculate the physical component score (PCS) and mental component score (MCS).

**Sleep**
Quality of sleep was assessed on a NRS, with score 0 indicating ‘no problems sleeping’ to score 10 ‘no sleep at all during the night’. Change of sleep quality compared with the baseline was assessed using a PGIC on a 7-point Likert scale. This measure is a single-item rating by patients of their improvement with the treatment during a clinical trial on a 7-point scale that ranges from ‘very much improved’ to ‘very much worse’ with ‘no change’ as the mid-point.

**Depressive symptoms**
The Becks’ Depression Inventory (BDI) questionnaire was used to investigate the presence of depressive symptoms. The BDI consists of 21 items rated on a 0-3 scale, thus scores range from 0 to 63. The BDI provides a well-accepted measure of the level of depressed mood in a sample and its response to treatment.

**Michigan Diabetic Neuropathy Score**
Before the start of the therapy, patients were classified according to the MDNS. The MDNS consists of a standardized neurological examination, including examination of vibration perception, pain perception, light touch, tendon reflexes and muscle strength, plus standard nerve conduction study (NCS) findings (Synergy and Viking NCS Systems, Carefusion, the Netherlands) performed on the non-dominant side assessing two motor nerves (peroneal and median) and three sensory nerves (sural, median, and ulnar). In motor nerves, the compound muscle action potentials following distal and proximal stimulation, terminal latencies, and conduction velocities were determined. In sensory nerves, action potential amplitudes, peak latencies, and conduction velocities were assessed. A nerve was considered abnormal if any attribute was not within the normal limits, defined as the values between the first and 99th percentiles.

**Clinical sensory testing**
A modified version of the Inflammatory Neuropathy Cause And Treatment (INCAT) study group sensory sum score (md-ISS) was used to assess the sensory function. The md-ISS ranges from 0 (no sensory deficit) to 33 (most severe sensory deficit) and is composed by the summation of assessment of pin prick sensation, vibration sense, light touch, joint position, and two-point discrimination.

**Pain characteristics**
The neuropathic pain scale (NPS) was used for the assessment of distinctive pain characteristics on a 0–10 NRS.

**Statistical analysis**
Statistical analyses were performed to test the changes in outcome measures using the Wilcoxon matched pairs test according to the intention-to-treat (ITT) principle. Additionally, patients who received a definitive pulse generator after positive trial stimulation are analysed in a received treatment (RT) analyses. Since no baseline values are available for PGIC, only descriptive statistics are presented. Differences between the responders and non-responders were analysed using the Mann–Whitney U-test. The statistical significance was defined as P<0.05. Given the exploratory nature of the study, no correction for multiple comparisons was performed. The statistical analysis was performed using SPSS 17.0 (Windows XP).

**Results**
Between January and June 2009, 27 patients were screened of which 19 patients met all eligibility criteria. Four patients refused to take part in the study: work-related reasons for rejection of study participation (two patients), pain relief after switching from oral antidiabetic agents to insulin (one), and effort to participate was too high (one). Informed consent was obtained from 15 patients (Table 1). The data from 15 patients were assessed at the baseline and 2 weeks, and from 14 patients at 12 months (one patient was lost during the follow-up). Eleven patients who received a definitive pulse generator after successful trial stimulation were included in the RT analysis at all time points (see Results section ‘Paraesthesia coverage, trial stimulation, and complications’).
reduction in the pain intensity during daytime was achieved in 8 patients (53%) at 2 weeks and in 7 patients (47%) at 12 months. Clinically relevant relief of nocturnal pain was achieved in 7 patients (47%) at 2 weeks and 3 patients (20%) at 12 months. Maximum pain intensity was significantly reduced in 9 patients (60%) at 2 weeks and in 3 patients (20%) at 12 months. Relevant improvement of painful symptoms on the PGIC for pain was achieved in 10 patients (67%) at 2 weeks and 9 patients (60%) at 12 months. In RT analysis on PGIC, relevant improvement was reported by 10 patients at 2 weeks and 3 months (91%), in 8 (73%) at 6 months, and in 9 patients (82%) at 12 months (Fig. 2A). Relevant worsening of painful symptoms was reported by one patient (9%) at 3 months.

Overall ITT analyses showed that SCS was successful in 11 patients (73%) at 2 weeks and in 10 patients (67%) at 12 months (Fig. 3).

Paraesthesia coverage, trial stimulation, and complications

Adequate paraesthesia coverage performed with one octa-lead in the painful area in both legs was achieved during the implantation procedure in 14 patients (93%) and trial stimulation was successful in 11 patients (73%). No complications or adverse events were encountered in this phase. During long-term follow-up lead displacement occurred in one patient, requiring adjustment of stimulation parameters.
In general, adaptation of stimulation characteristics was performed in 9 out of 11 patients during 12 months follow-up to optimize paraesthesia coverage and pain relief. In total, 21 adaptations were performed [mean 2.3 (range 1–5)].

**Quality of life**

In the ITT analysis, the EQ-5D utility score increased at 2 weeks. Thereafter, no statistically significant increase persisted (Fig. 4). In RT analysis, the EQ-5D utility score increased at 2 weeks and 3 months, after which the increase was no longer statistically significant. SF-36 PCS increased at 12 months compared with the baseline (Supplementary Fig. S1 online). No changes were observed in the SF-36 MCS in both ITT and RT analyses. In RT analysis, SF-36 PCS was increased compared with the baseline [35.5 (26.7–40.1)] at 3 months and 12 months, \( P < 0.01 \), but not at 2 weeks and 6 months.

**Sleep**

In the ITT analysis, quality of sleep improved from 6.0 (3.0–7.0) at baseline to 2.5 (1.0–3.0; \( P < 0.01 \)) at 2 weeks and 4.0 (1.0–5.3; \( P = 0.04 \)) at 12 months. In the RT analysis, quality of sleep improved from 6.0 (3.0–7.0) at baseline to 2.0 (1.0–3.0; \( P = 0.007 \)) at 2 weeks, 3.0 (0.0–4.0; \( P = 0.02 \)) at 3 months, 5.0 (2.5–7.0; \( P = 0.09 \)) at 6 months, and 4.0 (1.0–5.0; \( P = 0.02 \)) at 12 months.

Seventy-four per cent of patients reported significant improvement of sleep at 2 weeks and 12 months. In the RT analysis, significant improvement of sleep compared with the baseline was reported on the PGIC at 2 weeks by 7 patients.
67% (64%), at 3 months by 8 patients (73%), at 6 months by 5 patients (45%), and at 12 months by 7 patients (64%) (Fig 2a). Deterioration of sleep was reported by 2 patients (18%) at 6 months.

**Depressive symptoms**

In the ITT analysis, the BDI score decreased from 10.0 (6.0–13.0) at baseline to 7.1 (3.0–9.0; P<0.01) after 2-week trial stimulation. At 12 months, the BDI score was not different from baseline [7.0 (6.0–14.0; P=0.43)]. In the RT analysis, the BDI score decreased from 10.0 (7.0–14) to baseline to 7.0 (3.0–8.0; P=0.02) at 2 weeks and 7.0 (5.0–8.0; P=0.02) at 3 months. At 6 months [7.0 (4.0–19.0; P=0.30)] and at 12 months [7.0 (6.0–16.0; P=0.46)], the BDI score was not different from baseline.

**Michigan diabetic neuropathy score**

At baseline, mild neuropathy according to the MDNS was present in 6 patients (40%) and moderate-to-severe neuropathy was present in 9 patients (60%; Table 1). The severity of neuropathy was not different in responders compared with non-responders (P=0.57).

**Sensory testing**

Median mdISS before start of SCS treatment was 5.0 (3.0–9.0; range 0–19). No differences were found in the mdISS or individual components of the mdISS between responders and non-responders.

**Neuropathic pain characteristics**

At 12 months, a decrease on eight items of the NPS was observed in both ITT and RT analyses, including items describing general dimensions of pain (intensity of pain and unpleasantness), spatial dimensions (i.e. deep pain and surface pain) as well as pain quality domains (i.e. itching, sharpness, hotness, dullness) (Supplementary Fig. S2 online).

**Discussion**

Our pilot study shows clinically relevant pain relief in 67% of PDP patients after 1 year of SCS treatment. Furthermore, this is the first study indicating that SCS in PDP is associated with an improvement of quality of life, decrease of several pain characteristics, and improvement of sleep. Finally, this study could not find an indication that SCS treatment outcome can be predicted by clinical sensory testing.

Pain relief persisted in 67% of patients after 1 year which is in accordance with earlier reports.7 9 Studies indicate that the pain-relieving effect of SCS in PDP persists over time; however, the numbers of patients in the long-term follow-up studies are small.8 9

Adequate paraesthesia coverage of the painful area in both legs, which is generally considered a requisite for SCS efficacy, could be achieved in most patients with one SCS lead. However, lack of complete coverage of the feet did not preclude adequate pain relief. This is important, since the need for a second SCS lead to achieve complete coverage of the feet would increase the treatment costs substantially. No serious adverse events were encountered during the study period.

Since SCS is an invasive and expensive treatment modality, careful selection of appropriate patients for SCS therapy is important. Exclusion of peripheral arterial disease (PAD) is particularly important, since PAD is common in patients with diabetes and symptoms may be similar to PDP. Exclusion of PAD by the Fontaine classification is insufficient,9 since asymptomatic PAD is present in 29% of patients with diabetes28 and nocturnal pain (by definition Fontaine stage III) is a common symptom in PDP. Therefore, adequate exclusion of PAD is mandatory. Furthermore, selection of patients with a good chance of responding to SCS treatment is essential. At present, trial stimulation is performed to select patients with good initial SCS effect to receive a definitive pulse generator. The success rate of SCS after positive trial stimulation ranged from 71 to 78% in earlier studies7,9 to 91% in the present study. This difference might be explained by the different definitions of treatment success.

Nevertheless, more reliable and preferably non-invasive predictors of the SCS treatment outcome are needed. Large fibre dysfunction measured with somatosensory evoked potentials has been found to predict the SCS treatment failure in patients suffering from various neuropathic pain syndromes; however, this study did not include PDP patients.29 SCS efficacy was found to be decreased in patients with severe brush evoked allodynia due to CRPS,30 also suggesting a role of large fibre dysfunction in the SCS failure. However, we found no difference in large fibre function between responders and non-responders to SCS therapy, measured with NCS and clinical sensory testing. This difference might be explained by the different methods used to assess large fibre function and differences in the population studied. The role of large fibre function in the effect of SCS might be different in patients suffering from PDP compared with other pain syndromes. Furthermore, the number of patients might be too small to assess differences between responders and non-responders. Therefore, additional large-scale studies are needed to search for reliable predictors of the SCS treatment outcome.

**Conclusion**

SCS appears to be an effective and feasible treatment for intractable PDP. SCS is associated with improvement of quality of life, neuropathic pain characteristics, sleep, and with clinically relevant pain relief in two-thirds of patients. This study could not find an indication that the SCS treatment outcome can be predicted by clinical sensory testing. A large-scale RCT is needed to provide definitive high-quality proof of the, short-term and long-term, beneficial effects of SCS in PDP.

**Supplementary material**

Supplementary material is available at British Journal of Anaesthesia online.
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Declaration of interest

None declared.

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