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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 description[10] 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 $\geq$12 months; (ii) previous unsuccessful drug treatments [including tricyclic antidepressants, alpha-2-delta agonist (pregabalin or gabapentin), dual serotonin and noradrenalin receptor inhibitor]; (iii) an average pain intensity during day or night of $\geq$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 $\geq$II); unstable blood glucose control (HbA1c variation $\geq$1% over 3 month period).

Implantation of the SCS system

Using local anaesthesia and antibiotic prophylaxis (cefuroxime/erythromycin), an octapolar SCS lead (Octad® lead, 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.

Table 1 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

Patient characteristics	
Gender, *N* (male/female)	8/7
Age (yr) (range)	59.9 (50–72)
Baseline characteristics	Mean (SD)
Duration DM (yr)	15.0 (18.4)
Duration neuropathy (yr)	10.0 (13.3)
Duration painful symptoms (yr)	4.9 (3)
BMI (kg m^{-2})	28.8 (3.2)
MDNS	
No neuropathy	0 (0%)
Mild neuropathy	6 (40%)
Moderate neuropathy	7 (47%)
Severe neuropathy	2 (13%)
md-ISS	6.8 (5.0)

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