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Clinical note

Spinal cord stimulation in patients with painful diabetic neuropathy: A multicentre randomized clinical trial

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ABSTRACT

Painful diabetic neuropathy (PDN) is a peripheral neuropathic pain condition that is often difficult to relieve. Spinal cord stimulation (SCS) is a proven effective therapy for various types of mixed neuropathic conditions, yet effectiveness of SCS treatment for PDN is not well established. To our knowledge, ours is the first multicentre randomized controlled trial investigating the effectiveness of SCS in patients with PDN. Sixty patients with PDN in the lower extremities refractory to conventional medical therapy were enrolled and followed for 6 months. They were randomized 2:1 to best conventional medical practice with (SCS group) or without (control group) additional SCS therapy, and both groups were assessed at regular intervals. At each follow-up visit, the EuroQoL 5D, the short form McGill Pain Questionnaire (SF-MPQ) and a visual analogue scale (VAS, ranging 0–100) to measure pain intensity were recorded. The average VAS score for pain intensity was 73 in the SCS group and 67 in the control group at baseline. After 6 months of treatment, the average VAS score was significantly reduced to 31 in the SCS group ($P < .001$) and remained 67 ($P = .97$) in the control group. The SF-MPQ and EuroQoL 5D questionnaires also showed that patients in the SCS group, unlike those in the control group, experienced reduced pain and improved health and quality of life after 6 months of treatment. In patients with refractory painful diabetic neuropathy, spinal cord stimulation therapy significantly reduced pain and improved quality of life.

1. Introduction

Diabetes mellitus is a chronic disease characterized by chronic hyperglycaemia and defects in insulin secretion, insulin action, or both. Diabetes can result in peripheral polyneuropathy in up to 50% of patients [25]. Up to 15% of the diabetic population develops painful peripheral neuropathic symptoms, mainly affecting the lower limbs [19,22,25]. Although new drugs targeting neuropathic pain have become available over the last decades, only about one third of the patients with painful diabetic neuropathy (PDN) obtain more than 50% pain relief with the use of medication [11]. This motivates the need for alternative therapies to target PDN.

Spinal cord stimulation (SCS) is an invasive treatment for chronic pain based on electrical stimulation of the dorsal columns of the spinal cord. The mechanisms of action have not been fully elucidated but are believed to involve both spinal and supraspinal effects [1,15,23]. Generally, implantation of the SCS device consists of 2 phases. First, the electrode lead is implanted in the epidural space and connected to a temporary pulse generator outside the body (the trial phase). Only if the treatment provides significant

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pain reduction will the external pulse generator be replaced by an implanted pulse generator; otherwise the lead is removed and no SCS therapy is provided.

SCS has been shown to be an effective treatment for various mixed neuropathic pain conditions [16]. Although SCS is increasingly accepted in the treatment of failed back surgery syndrome [11,14], complex regional pain syndrome I [12], and angina pectoris [4,17], evidence of the effectiveness of SCS treatment in PDN is sparse; to date, there have been no randomized, controlled studies in this population.

A number of small uncontrolled studies have investigated the effects of SCS in patients with PDN, with encouraging results [3,7,13,21,24]. The study carried out by Tesfaye et al. in 10 patients demonstrated significant pain relief for at least 1 year in 7 of them [24]. Long-term follow-up of 4 of these patients was performed by Daousi et al. and showed continued pain relief after 7 years of stimulation [3]. Kumar et al. reported on 4 patients who had peripheral neuropathy due to diabetes [13]. All 4 patients obtained good results in terms of pain relief on the short term (3 months) and 3 out of 4 on the long term (12 months or longer). De Vos et al. carried out an SCS study in 11 patients with PDN [7] in which 9 patients were converted to a permanent system. Pain intensity and analgesic medication were reduced significantly up to 30 months after implantation. Similar encouraging results were found in a pilot study by Pluijms et al. [21].

In order to thoroughly investigate the effect of SCS in PDN, we performed what is to our knowledge the first prospective multicentre randomized clinical trial comparing the efficacy of SCS therapy to best conventional medical practice.

2. Methods

The present study was an open randomized parallel-group design. Patients were randomized in a 2:1 fashion to either best medical therapy with SCS or best medical therapy alone. Patients were recruited from 7 pain clinics in the Netherlands, Denmark, Belgium, and Germany and were evaluated and diagnosed with diabetic neuropathy by their referring neurologist. The study conformed to the Declaration of Helsinki and was approved by each centre's institutional review board or ethics committee. All patients provided informed consent before participation. The study was registered at the Dutch Trial Register (ISRCTN03269533).

2.1. Patients

Between November 2008 and October 2012, a total of 60 patients were included and, stratified for sex, randomly assigned to best conventional medical practice with (SCS group) or without (control group) additional SCS therapy. The randomization was a block stratified randomization per centre, as 1 centre included 24 patients and the other centres included between 2 and 13 patients. Eligible patients were at least 18 years of age and had refractory diabetic neuropathic pain in the lower extremities for more than 1 year. All conventional pain treatments had been tried, and the patients could not be treated any further according to their referring medical specialist, but had still an average pain score on a visual analogue scale (VAS) of at least 50. Even though SCS has shown to be an effective therapy in cases of peripheral vascular disease [5], patients with pain due to atherosclerotic lesions were excluded to avoid doubt regarding which pain aetiology was being treated. Patients were also excluded from participation in the study if they had an infection, had neuropathic pain in their upper extremities (VAS score of more than 20 while at rest), received anticoagulant medication or had known coagulation irregularities, had psychiatric problems (eg, depression) requiring treatment, had an addiction to drugs or alcohol, or were incapable of cooperation.

2.2. Study procedure

Patients were randomized to either the SCS group or the control group. For all patients in both groups, medication adjustments and other conventional pain treatments, such as physical therapy, were allowed at any time during the study, if needed. All changes in medication or other conventional pain treatments were registered. However, reduction and changes in medication were not part of the study protocol but rather were at the discretion of the treating physician. Implantation of the SCS system was performed according to each pain clinic's practice. Antibiotic prophylaxis was administered, and a trial stimulation period of 7 days maximum was allowed to test whether a patient responded positively to SCS. One electrode lead (Octrode or S8 Lamitrode; St Jude Medical, Plano, Tex) was implanted in the epidural space and positioned where the patient reported optimal overlap between paresthesia and the painful area, generally over the physiological midline, with the tip of the electrode lead between vertebral level T9 and T12. The lead was anchored to the fascia and connected through an extension to an external pulse generator (Multiprogram Trial Stimulator; St Jude Medical). If the trial period was successful, an implantable pulse generator (EonC, Eon, or Eon Mini; St Jude Medical) was implanted subcutaneously in either the anterior abdominal wall or the upper buttock and connected to the electrode lead that was also used during trial stimulation.

Evaluation visits were scheduled 1, 3, and 6 months after initiation of SCS treatment (SCS group) or enrolment (control group). After 6 months, patients in the control group who did not have adequate improvement could cross over to SCS therapy. After completion of the study period, all patients were followed in accordance with best medical care.

2.3. Outcome parameters

In order to evaluate the efficacy over time of the addition of SCS treatment to best medical practice, pain measures and other health outcome parameters were acquired at each study visit. The study's primary outcome parameter was the percentage of patients with more than 50% pain reduction at 6 months of treatment in each study group. Secondary outcome parameters were average reduction in pain intensity, pain characteristics and quality of life assessed by short form McGill Pain Questionnaire (SF-MPQ) [20] and EuroQoL 5D form (EQ5D) [8], respectively, and medication intake and patient global impression of change [9].

Pain scores were assessed using a VAS (with 0 representing no pain and 100 the worst pain imaginable), with the total number of words chosen from the McGill Pain Questionnaire (NWC), and the total pain rating index of these words (PRI). Health-related quality of life was evaluated using the self-reported perception of health from the EQ5D questionnaire (100 representing the best and 0 the worst health state imaginable) and questions about quality of life from the MPQ questionnaire (MPQ-QoL). The MPQ-QoL score increases when pain disturbs daily activities and sleep (0 represents the best and 27 the worst quality of life) [27].

The use of various types of analgesic medication was recorded and the Medication Quantification Scale III (MQS) [10,18] was used to evaluate the intake of analgesics. The MQS score for a single medication is calculated by multiplying a score for the used dosage by the detriment weight for its given pharmacological class. The total MQS score is the sum of all calculated values.

After 6 months, patients were also asked to indicate on a 4-point scale whether or not they would recommend the treatment they had to other patients with PDN, to rate on an 11-point scale their satisfaction with the treatment and to indicate their overall health and pain status on a 7-point patient's global impression of change scale. The safety and tolerability of SCS therapy over

time was evaluated using information on treatment-emergent adverse events, device complications, and premature withdrawal from the trial.

2.4. Statistical analysis

Based on previous randomized trials on SCS therapy for complex regional pain syndrome I [12] and failed back surgery syndrome [14], it was anticipated that about one third of the patients in the SCS group would not respond to trial stimulation and would therefore not receive a stimulator. Based on the results from the pilot study by de Vos et al. [7], the percentage of patients with more than 50% pain reduction was assumed to be 50% in the SCS group vs 10% in the control group. These estimated response rates and a desired 90% power to find a difference between the 2 groups at a 5% level of significance required a sample size of 60 patients for a 2:1 randomization between the SCS and control groups. For all outcome measures, values at baseline and after 6 months of treatment were calculated for patients in both groups. An intention-to-treat analysis was performed, and missing data were imputed by carrying forward earlier values. The values of the 2 groups were compared with the use of 2-tailed Student's *t* tests for independent samples. To detect treatment effects within a group, paired-sample *t* tests were performed. Additional analyses were performed using Fisher's exact test for categorical variables (SPSS software, version 15; IBM, Armonk, NY). Randomization and data management were performed by an independent third party, and data analysis on the anonymized data was performed by the first author at the University of Twente, the Netherlands.

3. Results

3.1. Patients

Sixty patients with PDN were enrolled and randomized to SCS ($n = 40$) or control ($n = 20$) treatment. Baseline characteristics were relatively well balanced between the 2 groups, the main exceptions being a somewhat higher age and lower pain score in the control group. However, none of the differences between the groups was significant (Table 1).

In the SCS group, 3 patients did not have successful trial stimulation. In 1 patient, it was not possible to implant the electrode lead in the epidural space, and 2 patients did not perceive significant pain relief. All 3 dropped out of the study immediately. One patient responded well to SCS therapy but was withdrawn after 3 months when he decided to enter a pharmacological gastroenterology study as well. The remaining 36 patients completed their 6-month follow-up visit. In the control group, 2 patients dropped out after 3 months because of new diseases that were unrelated to the study but that were stressful for the patients. These patients withdrew their consent, and thus 18 patients were followed for 6 months.

No data were available from patients after they dropped out and because of holidays, sickness, or logistic reasons, 2 patients (control group) missed their 1-month follow-up visit and 4 patients (2 SCS and 2 control group) missed their 3-month follow-up visit. Data analyses were performed on patients with a complete data set as well as on patients with an incomplete data set but whose data were imputed by carrying forward earlier values.

Table 1
Baseline patient characteristics.

Characteristic	SCS ($n = 40$)	Control ($n = 20$)
Sex, n		
Female	15	7
Male	25	13
Diabetes, n		
Type I	10	5
Type II	30	15
Age, y, average (SD)	58 (11)	61 (12)
Duration of diabetes, y, average (SD)	16 (11)	17 (12)
Duration of pain, y, average (SD)	7 (6)	7 (6)
Pain, VAS, average (SD)	73 (16)	67 (18)
Quality of life, MPQ score, average (SD)	16 (5)	15 (6)
Self-reported health, VAS, average (SD)	50 (19)	47 (17)
Pain medication, MQS, average (SD)	10.6 (9.7)	9.2 (7.8)

SCS, spinal cord stimulation; MPQ, McGill Pain Questionnaire; VAS, visual analog scale; MQS, Medication Quantification Scale III.

3.2. Primary outcome measures

As shown in Fig. 1a, mean pain scores at enrolment were comparable for the 2 groups. After 1 month of SCS, the mean VAS pain score for the SCS group was reduced to 29 (SD 28) and was stable throughout the remainder of the study period. After 6 months, 25 patients in this group had over 50% pain reduction (Table 2), 16 of whom had a reduction of more than 75%. In the control group, the average pain score remained stable, and only 1 patient exhibited a pain reduction of more than 50%.

3.3. Secondary outcome measures

At baseline, patients in both groups used 13 words on average from the McGill pain questionnaire to describe their pain. Words like "stabbing," "cutting," "burning," "scalding," "sharp," and "exhausting" were most often used. After 6 months, the average number of words used (NWC) dropped significantly to 8 in the SCS group, while in the control group the total number of words remained 13. Besides fewer words, patients in the SCS group generally also used words describing less intense sensations (PRI). In most cases the sharp, cutting, and scalding component of the pain was reduced, which made the pain more bearable.

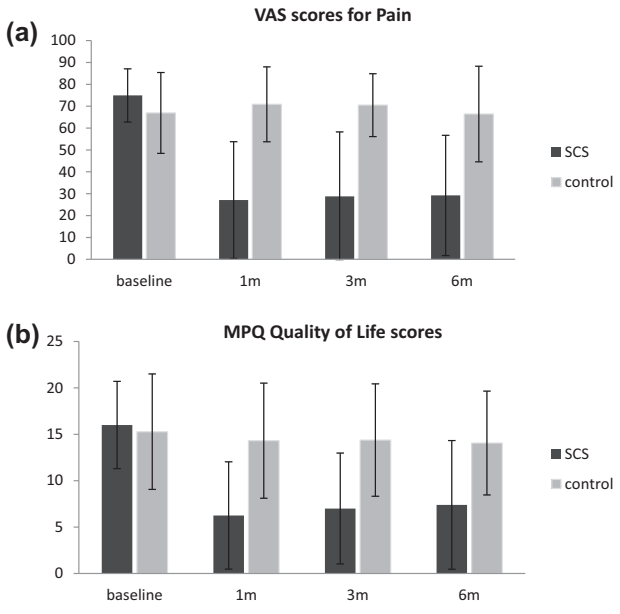

Fig. 1. (a) Average pain scores for the SCS treatment group (dark grey) and control group (light grey) at baseline and after 1, 3, and 6 months of treatment; high score corresponds with severe pain. (b) Average McGill Pain Questionnaire Quality of Life scores; high score corresponds with severely disturbed daily activities and sleep. Error bars represent standard deviation.

Table 2
Outcome measures for study groups at baseline and after 6 months of treatment (intention-to-treat analysis).

Characteristic	SCS		Control	
	Baseline (n = 40)	6 mo (n = 40)	Baseline (n = 20)	6 mo (n = 20)
Pain				
Mean VAS (SD)	73 (16)	31 (28)***	67 (18)	67 (21)^^^
Absolute VAS reduction (SD)		42 (31)		0 (20)^^^
Relative VAS reduction (SD)		55% (41)		0% (47)^^^
>50% pain reduction n (%)		25 (60%)		1 (5%)^^^
MPQ mean NWC-T (SD)	13 (5)	8 (7)***	13 (3)	13 (4)^^
MPQ mean PRI-T (SD)	27(13)	15 (14)***	24 (9)	26 (10)^^
Analgesics				
MQS, mean (SD)	10.6 (9.7)	7.7 (8.7)***	9.2 (7.8)	10.1 (8.2)
Opioids, n (%)	18 (45%)	15 (38%)	11 (55%)	11 (55%)
NSAIDs, n (%)	6 (15%)	3 (8%)	2 (10%)	2 (10%)
Antidepressants n (%)	14 (35%)	13 (33%)	9 (45%)	8 (40%)
Anticonvulsants n (%)	23 (58%)	18 (45%)	7 (35%)	7 (35%)
Acetaminophen n (%)	12 (30%)	7(18%)	6 (30%)	6 (30%)
No analgesics n (%)	6 (15%)	9 (23%)	3 (15%)	1 (5%)
Quality of life				
MPQ QoL score, average (SD)	16 (5)	8 (7)***	15 (6)	14 (6)^^^
EQ5D self-reported health, average (SD)	50 (19)	61 (22)*	46 (17)	41 (20)^^
PGIC pain reduction, n (%)		29 (73%)		3 (17%)^^^
Satisfaction with treatment		8/10		4/10^^^

SCS, spinal cord stimulation; VAS, visual analog scale; NWC-T, McGill Pain Questionnaire; PRI-T, pain rating index; NSAID, nonsteroidal anti-inflammatory drug; MPQ, McGill Pain Questionnaire; MQS, Medication Quantification Scale III; QoL, quality of life; EQ5D, EuroQoL 5D; PGIC, patient global impression of change.
*P < .05, ***P < .001 (significant treatment effect within a group); ^^P < .01, and ^^^P < .001 (significant treatment effect between groups).

Fig. 1b shows that at baseline the average MPQ-QoL scores for both groups were comparable and about 70% of the patients in both groups reported disturbed sleep. After 6 months, 12 patients (30%) in the SCS group and 13 patients (65%) in the control group had still problems sleeping. In addition, the average EQ5D self-rated health score increased in the SCS group and decreased in the control group.

At baseline, patients in both groups used opioids, anticonvulsant medication, antidepressants, nonsteroid anti-inflammatory drugs, and acetaminophen. A large majority of patients used combinations of various analgesics (Table 2), although 9 patients had chosen not to use any prescribed pain medication due to unacceptable adverse effects combined with only limited therapeutic effects. After 6 months, the SCS group had a statistically significant improvement in MQS score, which indicates a significant reduction in analgesic intake.

All patients in the SCS group could adjust the stimulation amplitude to their own convenience and were allowed to switch the stimulation off and on as they wished. About 10% of the patients had a cyclic stimulation programme, with 15 s stimulation on and 15 s stimulation off, but due to delayed sensations, they did not sense the off periods and had stable pain reduction. The majority of the patients used the stimulation continuously, and a few of them never adjusted the stimulation amplitude.

In the SCS group, 26 patients (65%) stated that they had much or very much pain reduction at 6 months compared to baseline, and 3 patients (8%) indicated some pain reduction. Only 3 patients (15%) from the control group indicated some pain reduction; despite receiving the best conventional pain treatment, 8 patients (40%) perceived an increase in pain. In the SCS group, of the 37 patients with an implanted SCS system, all but 2 patients (n = 35, 95%) might or would definitely recommend SCS treatment to other patients with PDN; in the control group, only 4 patients (20%) might recommend conventional pain treatment to other patients. Patients in the SCS group were on average content with the treatment they received, while patients in the control group were generally not content (Table 2).

3.4. Adverse events

Taking into account the condition of our patient population and the invasive nature of the SCS procedure, only a few adverse events and complications have occurred during the study period. Adverse events that were not related to the study procedure but mainly to diabetes-related health issues occurred in both groups to the same amount. In the SCS group, the adverse events were as follows: 2 infections causing unstable blood glucose levels, 1 femur fracture, and 1 cardiac arrest. In the control group, there were 2 infections, 1 carotid artery stenosis, 1 myocardial infarction, 1 atrial fibrillation episode, and 1 coronary bypass surgery. All these adverse events were treated and improved or resolved during the study period.

Adverse events related to the implantation procedure were generally resolved by device repositioning. These included pain due to the implanted pulse generator in 2 patients and electrode lead migration in 1 patient. Two patients perceived incomplete overlap of the paresthesia with the painful area during trial stimulation, and they had a second electrode lead directly placed. There was 1 infection during trial stimulation, which was successfully resolved and followed by a permanent implantation. Finally, 1 patient turned out to have coagulopathy, which complicated the implantation procedure and prolonged hospitalization.

4. Discussion

Previously, only small nonrandomized studies have investigated the effects of SCS in patients with PDN, although all had promising results [3,7,13,21,24]. The present study is, to our knowledge, the first randomized trial demonstrating that SCS therapy causes a highly clinical significant pain reduction in patients with refractory diabetic neuropathic pain. Trial stimulation was successful in 37 of 40 (93%) patients with PDN. These patients received an implantable pulse generator, and SCS therapy reduced their average pain intensity by 60%, whereas in the control group, conventional pain treatment did not change the pain intensity at

all. The percentage of patients that experienced a pain reduction of more than 50% after 6 months of SCS was 65%, while only 1 patient (5%) in the control group perceived such a pain reduction.

These findings are comparable with the findings in previous studies in patients with PDN. Already in 1996, Kumar et al. [13] showed successful trial stimulation in all 4 patients (100%) and 3 of these patients (75%) experienced over 50% pain relief on the long term (12 months or longer). In that same year, Tesfaye et al. obtained significant pain relief during trial stimulation in 8 of 10 (80%) patients and over 50% pain relief for at least 1 year in 7 of them [24]. Long-term follow-up of 6 of these patients was performed by Daousi et al. [3], revealing continued over 50% pain relief after 3 years of stimulation in 5 patients. The pilot study by de Vos et al. [7] showed that 9 of 11 (82%) patients had successful trial stimulation, and that after 12 months over 50% pain reduction was still obtained in 7 patients.

In the current randomized study, 95% of the patients in the SCS group might or would definitely recommend SCS treatment to other patients with PDN, while 73% of the patients stated that they had some, much, or very much pain reduction. This means that some patients who said that they perceived no pain reduction would still recommend SCS, which indicates that SCS might have other beneficial effects besides pain reduction. Our study shows that after 6 months of SCS, many patients feel healthier, have improved sleep, and/or have been able to reduce their analgesic intake.

The study demonstrated that in addition to pain reduction and improvement in quality of life, SCS therapy reduced intake of pain medication, while conventional pain treatment did not. Mainly as a result of adverse effects of the analgesics, many participants in the study were motivated to reduce their analgesic intake. Although the improvement in MQS score was statistically significant, reduction in analgesics was not as dramatic as it was in the pilot study, where more than 50% of the patients terminated their analgesic intake [7]. However, in the pilot study, reduction or change in medication was part of the study instruction, and medication was adjusted by the researchers. In the current study, changes in medication were entirely at the discretion of the individual treating physician. It is possible that patients in the current study had more severe health-related problems caused by diabetes mellitus than the patients in the pilot study, which may have limited the possibilities for medication reduction.

A limitation of the present study is that the study was an open-label design. Patients in both groups had already received all possible kinds of conventional treatment and could not be treated any further according to their referring physician. Despite the efforts that were made to further optimize their conventional treatment, many patients in the control group did not perceive any improvement, and all of them were aware that they would be offered trial SCS after 6 months. It cannot be ruled out that some of the data collected in this group were biased by this prospect.

In the SCS group, pain reduction after 1 month of SCS therapy was already significant and was maintained over the 6-month study period. These sustainable results, comparable with previous case reports [3,7,13,21,24], in a patient population that has already received multiple other therapies, all with little success, suggest that it is unlikely that the pain reduction caused by SCS is merely a placebo effect. However, as with every form of treatment, placebo effects can never be ruled out completely. A placebo-controlled trial in which both patient groups receive the device and only 1 receives active treatment seems to be feasible with new paresthesia-free stimulation protocols [6,26]. However, the large difference in energy consumption between paresthesia-free stimulation and placebo treatment would reveal the treatment arm within days, as patients with paresthesia-free stimulation would need to recharge their implanted pulse generator, where patients with placebo treatment would not.

Patients with diabetes mellitus are susceptible to infections, so a short trial period is prudent.

On the other hand, we experienced that as a result of their disturbed sensory perception, it can take hours before a patient will feel changes in sensation caused by changed SCS settings. Patience and careful consideration regarding lead positioning and duration of the trial period are therefore necessary. According to a review on SCS by Compton et al. [2], infections occur in up to 8% of the patients, while lead complications occur in up to 30% of the patients. The incidences of infection and lead complications in the SCS group were 3% and 8%, respectively. Hence, despite our patients' health-related problems, the incidence of device- and procedure-related adverse events is low and compares favourably to other SCS trials.

In conclusion, the present study demonstrated that, compared with conventional pain treatment, spinal cord stimulation reduces pain significantly and improves the quality of life in patients with refractory painful diabetic neuropathy in the lower extremities.

Conflict of interest

Dr K. Meier received teaching fees from St Jude Medical and is a paid consultant for Biolab Technology. The other authors report no conflict of interest.

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