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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