

Electrical spinal-cord stimulation for painful diabetic peripheral neuropathy

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Summary

Background Conventional treatment for painful peripheral diabetic neuropathy is largely symptomatic and often ineffective, with unacceptable side-effects. We tested electrical spinal-cord stimulation for the management of chronic neuropathic pain.

Methods Ten diabetic patients who did not respond to conventional treatment (mean age 51 [SD 9.3] years, six with type II diabetes, mean duration of diabetes 12 [6.3] years, mean duration of neuropathy 5 [2.1] years) were studied. The electrode was implanted in the thoracic/lumbar epidural space. Immediate neuropathic pain relief was assessed by visual analogue scale (VAS) after connecting the electrode, in a random order, to a percutaneous electrical stimulator or to a placebo stimulator. Exercise tolerance was assessed on a treadmill.

Findings Eight subjects had statistically significant pain relief with the electrical stimulator ($p < 0.02$) and were therefore converted to a permanent system. Statistically significant relief of both background and peak neuropathic pain was achieved at 3 months ($n=7$, $p=0.016$), at 6 months ($n=7$, $p=0.03$), and at the end of the study (14 months, $n=7$, background pain $p=0.06$, peak pain $p=0.03$). One patient died 2 months after the start of the study of unrelated cause while continuing to benefit from treatment and another patient ceased to benefit at 4 months. McGill pain questionnaire scores with the stimulator turned off did not change significantly from baseline scores, indicating that the severity of the underlying pain was unaltered. However, with the stimulator turned on, there was a statistically significant ($p < 0.05$) improvement in all four components of the score, by the end of the study. At the end of the study, six patients continued to gain significant pain relief and used the stimulator as the sole treatment for their neuropathic pain. For example, median background and peak pain scores at the end of study, were, respectively, 77 and 81 with the stimulator off and 23 and 20 with the stimulator on. Exercise tolerance significantly improved at 3 months ($n=7$, median % increase 85 [IQR, 62–360], $p=0.015$) and at 6 months ($n=6$, 163 [61–425], $p=0.0007$). Electrophysiological tests, vibration perception-threshold, and glycaemic control were unchanged.

Interpretation Electrical spinal-cord stimulation offers a new and effective way of relieving chronic diabetic neuropathic pain and improves exercise tolerance. The technique should be considered in patients with

neuropathic pain who do not respond to conventional treatment.

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Introduction

Peripheral neuropathy is a common long-term complication of diabetes.¹ About 7.5% of unselected adults attending a hospital diabetic clinic have painful neuropathic symptoms, mainly in the lower limbs.² Pain varies from mild paraesthesiae in a few toes to severe unremitting pain in both legs.^{2,3} Night-time exacerbation of the pain plus contact hypersensitivity to bed-clothes results in loss of sleep, and pain in diabetic neuropathy can be disabling.³

The cause of chronic sensory-motor diabetic neuropathy or indeed neuropathic pain is not known although metabolic and microvascular systems may be involved.^{4–6} Whilst the search for potential therapeutic agents to halt or reverse the neuropathic process continues,⁷ current treatment is largely aimed at relieving painful symptoms. However, conventional drugs are often ineffective and complicated by side-effects.⁸

This situation led us to explore electrical spinal-cord stimulation (ESCS) for the treatment of chronic diabetic neuropathic pain that did not respond to conventional drugs. ESCS has been used for several chronic painful conditions, including back pain, phantom-limb pain, peripheral vascular disease, and severe angina.⁹

Patients and methods

Patients

We studied ten patients with chronic sensory-motor diabetic neuropathy (six with type II diabetes, mean age 51 [SD 9.3] years, duration of diabetes 12 [6.3] years). All had severe symptomatic neuropathy (mean duration of pain 5 [2.1] years) that was unresponsive to conventional drugs. All were male, and gave informed consent. The study was approved by the local ethical committee.

Patients underwent the following assessments at baseline and at 3 and 6 months: (1) full history and examination, which included assessment of neuropathic symptoms and deficit scores; (2) ankle pressure-index with a doppler ultrasound stethoscope (BF4A, Med Sonics, Mountain View, California, USA); and (3) vibration perception-threshold (VPT) over the index fingers, great toes, and medial malleoli (Biothesiometer, Biomedical Instrument Co, Newbury, Ohio, USA). Motor (median, ulnar, peroneal, and tibial) and sensory (median, ulnar superficial peroneal, and sural) nerve conduction-velocities were measured at a skin surface-temperature of 33 [1]°C (Nicolet Viking IV, Nicolet Instruments, Warwick, UK), at baseline and at 6 months. In addition a graded exercise-tolerance was tested on a treadmill with the Naughton protocol¹⁰ at baseline, 1, 3, and 6 months. One patient was unable to use a treadmill because of unsteadiness, and so walking distance on the flat was recorded as a measure of exercise threshold. Exclusion criteria included peripheral vascular disease with absence of foot pulses or ankle pressure-index below 1, presence of active foot-ulceration, treatment with anticoagulants, neuropathic pain of less than 1

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year's duration, neuropathic pain in upper limbs, and presence of peripheral neuropathies from causes other than diabetes (normal renal function except in one patient who had painful neuropathy before development of mild renal impairment: serum creatinine 134 $\mu\text{mol/L}$, normal serum B_{12} , no excess alcohol consumption, not on neurotoxic drugs). Neuropathy was staged with Dyck's scoring and all cases had stage 3, severe symptomatic/disabling neuropathy.¹¹ All had previously been started on tricyclic antidepressants and anticonvulsants for painful neuropathy although in some these had been stopped because of side-effects. All were receiving treatment at enrolment (8 on tricyclic antidepressants, 6 on anticonvulsants, 3 on mexiletine, 2 on non-steroidal anti-inflammatories, 2 on dihydrocodeine plus paracetamol).

Initial trial of ESCS

All the patients were admitted and baseline background pain was assessed by visual analogue scale (VAS) 4 hourly for 2 days while taking their usual pain-relieving drugs. Ward nurses used a 10 cm ruler marked "no pain" at one end and "worst pain ever" at the other, and calibrated on a side patients could not see, to record intensity of pain. Peak pain, which is the worst pain experienced over the previous 4 hours, was also assessed by VAS. On day 3, an ESCS electrode (PISCES-Quad Plus, model 3888, Medtronic Ltd, Watford, Herts, UK) was inserted into the epidural space. Five patients had a placebo screener (stimulator) connected to the external end of the electrode for 2 days followed by an active screener (Medtronic 3625) for 2 days, and five had the active screener connected to the electrode followed by the placebo screener for 2 days. Stimulation was set to a level resulting in paraesthesias in the area of pain, but not sufficient to cause pain. The placebo screener was of similar size to the active screener but had a disconnected output and a series of lights controlled by a potentiometer to give an impression of activity. Background and peak pain were assessed as before.

At the end of the trial period, if there was improvement in pain scores (VAS reduction greater than 50%) that was considered clinically significant, a receiver (Medtronic X-Trel, model 3470) was implanted in the anterior abdominal wall and connected to the PISCES-Quad Plus lead already in place on day 10. Stimulation was continued by induction with an external radio-frequency transmitter (as below).

Because neuropathic pain can vary daily, the previous week's background and peak pain were scored by VAS, with the stimulator turned on and off, at 3 months, 6 months, and at the end of the study. Patients were given written instruction to think about the previous week's "average" background and peak pain with the stimulator turned on and off and to mark these. The McGill pain questionnaire¹² was recorded at baseline and at 3 and 6 months with the stimulator turned off, and at the end of the study with the stimulator turned on and off.

Surgical procedures

On the morning of day 3 after admission, a PISCES-Quad Plus stimulator lead was introduced into the epidural space via a 15-gauge Tuohy needle at L1-L2 in a neurosurgical operating theatre under local anaesthesia. Using an image intensifier, we manipulated the lead so that the electrode lay exactly midline on the dorsal aspect of the spinal cord. The lead had four platinum-iridium electrodes, 6 mm long and spaced 12 mm apart. The lead was connected to an external electrical stimulator and the final electrode position was determined by superimposition of induced paraesthesias to the area of pain, which was usually between T9 and T11.

On day 10, patients returned to theatre where, under local anaesthesia and sedation, a Medtronic X-Trel receiver was implanted in subcutaneous tissue in the right-lower anterior abdominal wall. An insulated extension was tunneled subcutaneously round the right flank to connect this receiver to the PISCES-Quad Plus lead. We stimulated by placing the antenna of the Medtronic model 3425 transmitter on the skin over the receiver. The transmitter uses a radio-frequency signal to transmit the prescribed stimulator information.

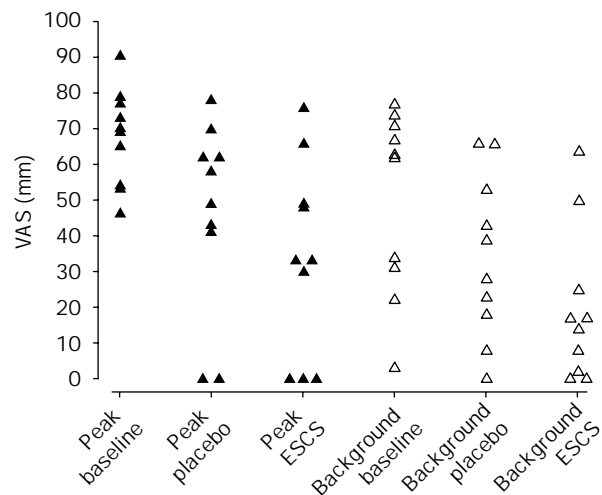


Figure 1: VAS pain scores

Peak (\blacktriangle) and background (\triangle) pain scores before insertion of spinal-cord stimulator wire (baseline), and with wire connected to placebo and active stimulator (ESCS), during trial stimulation. Peak pain: baseline vs placebo, $p=0.02$; baseline vs ESCS, $p=0.002$; placebo vs ESCS, $p=0.016$. Background pain: baseline vs placebo, $p=0.005$; baseline vs ESCS, $p=0.002$; placebo vs ESCS, $p=0.004$. (Wilcoxon's signed-rank tests).

Pain control

Both the Medtronic screener, used to provide stimulation during the initial trial phase, and the X-Trel transmitter allowed adjustment of several stimulator variables. The polarity of each electrode could be positive, negative, or turned off. At least one electrode had to be positive and one negative for current to flow, but with four electrodes we had fifty possible combinations. Electrode polarity controlled the level of paraesthesia. Pulse width could be adjusted from 50 to 1000 μs and controlled the size of the area of paraesthesia. These two variables were adjusted by us. The patient controlled the frequency of stimulation from 5 to 1400 Hz (the preferred range was 50-120 Hz) and the intensity of stimulation by adjusting the amplitude from 0 to 10 V.

Patients were instructed to adjust the frequency and amplitude to induce strong but comfortable paraesthesia overlapping the painful area. In those patients who benefited from ESCS, pain sensations were masked by stimulation. The transmitter was turned on when there was pain or anticipation of pain. All the patients used stimulation freely when there was pain and throughout the night to have an uninterrupted night's sleep. All pain-relieving drugs used by the patients were stopped throughout the study.

Statistical analysis

All 4-hourly VAS scores were added in the 48-hour periods and divided by 12 to obtain mean scores. VAS pain scores and McGill pain questionnaire answers were analysed with Wilcoxon's matched-pairs signed-rank test. Changes in percent increase in exercise threshold were analysed by Mann-Whitney U test. We used Arcus Pro-Stat version 3.23. These tests were preceded by ANOVAs when appropriate.

Results

Pain scores

Background pain—The median (interquartile range [IQR]) baseline background VAS was 62.5 (28.8–71.8) mm. Both placebo and the active stimulator improved background pain scores significantly compared with baseline: with placebo, 33.5 (15.5–56.3, $p=0.005$); and with active stimulator, 15.5 (1.5–31.3, $p=0.002$) (figure 1). However, the active stimulator improved pain scores significantly more than placebo ($p=0.004$).

Patient	Baseline		3 months				6 months				End of study				
	Background pain	Peak pain	Background pain		Peak pain		Background pain		Peak pain		Months since implant	Background pain		Peak pain	
			Off	On	Off	On	Off	On	Off	On		Off	On	Off	On
1	3	53	5	4	58	8	13	0	75	0	20	2	2	83	9
2	63	69	55	30	73	64	26	10	41	31	19	72	33	82	42
3	22	54	48	17	85	26	69	68	68	23	18	80	11	81	15
4*	31	46
5	71	79	75	62	79	65	88	88	90	90	6	88	88	90	90
6	62	65	90	50	90	53	70	45	80	60	14	73	32	71	23
7	77	73	76	49	84	52	55	29	80	45	11	77	23	81	17
8	34	77	70	10	78	10	73	0	72	0	9	84	23	79	10
Median	70	30	79	52	69	29	75	31	14	77	23	81	20
IQR	48-76	10-50	73-85	10-64	26-73	0-68	68-80	0-60	9-19	72-84	11-33	79-83	14-54
Signed-rank test			p=0.016		p=0.016		p=0.03		p=0.03			p=0.06		p=0.03	

*Patient 4 died 2 months after implant of unrelated cause. Patient 5 ceased to respond 4 months after implant.

Table: VAS background and peak pain scores (mm) with ESCS turned off and on

Peak pain—The median baseline peak pain VAS score was 69.5 (53.8–77.5). Both placebo and the active stimulator improved peak pain scores significantly compared with baseline: with placebo, 53.5 (30.8–64.0, $p=0.02$); and with active stimulator, 33.0 (0–53.0, $p=0.002$) (figure 1). Again the active stimulator improved peak pain significantly more than placebo ($p=0.016$).

Pain scores after implantation of X-Trel receiver (table 1)—8 of 10 patients scored pain as improved (VAS reductions greater than 50%) with the active stimulator and they were implanted with X-Trel receivers. Seven patients were followed up, one patient dying 2 months after electrode insertion, of unrelated cause. A second patient who gained statistically significant pain relief initially ceased to benefit from ESCS at 4 months and the wire was removed, but his pain scores were included in the statistical analysis at 6 months and at the end of the study. ESCS effectively controlled both background and peak pain at 3 months and 6 months and at the end of the study (table).

McGill pain questionnaire—With the stimulator turned off, there was no statistically significant change in any of

the four components of the questionnaire at 3 months, 6 months, and end of the study compared with baseline (except for the sensory components at 3 months, $p<0.05$). There was, however, a significant improvement in all four components with the stimulator turned on compared with it turned off at the end of the study ($p<0.05$).

Exercise threshold

There was a wide variation in exercise threshold, with five patients managing under 30 seconds and three patients managing 3 or more minutes on the treadmill. Figure 2 shows the mean percent increase in exercise time in all but one patient who could not be exercised on a treadmill and therefore had exercise distance measured on the flat. There was a non-significant improvement in exercise threshold at 1 month ($n=8$, median [IQR]% increase 1.25 [4–263], $p=0.08$), which became significant at 3 months ($n=7$, 85 [62–360]%, $p=0.015$) and at 6 months ($n=6$, 163 [61–425]%, $p=0.0007$).

Neurophysiological indices and metabolic control

At baseline, only the two patients who did not respond to ESCS at the initial trial stimulation had unrecordable VPTs (ie >50 V) in their feet, and one of these had an unrecordable VPT in his hands. There were no significant changes in VPT, nerve conduction velocities, and mean concentrations of glycated haemoglobin at 3 and 6 months compared with baseline.

Outcome and complications

Two patients failed to respond to ESCS during the initial trial phase. One patient died of an unrelated condition after 2 months while continuing to benefit from ESCS with an improved exercise threshold after 1 month. A fourth patient, who gained pain relief initially, failed to respond to ESCS after 4 months, despite continued projection of paraesthesias over the area of pain. This phenomenon of “late failure” is well described although the causes are not fully understood.¹³ The lead migrated in two patients, requiring reinsertion. Two patients required antibiotics for superficial wound infection after implantation of the receiver. At the end of the study, six patients continued to gain relief of pain and used the stimulator as the only treatment for their neuropathic pain, all pain-relieving drugs having been stopped.

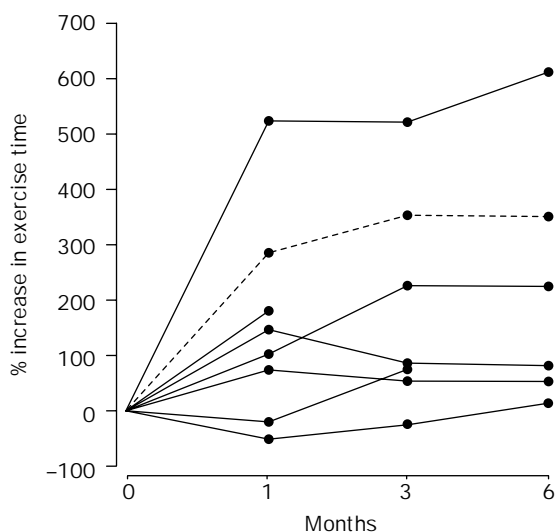


Figure 2: Exercise thresholds
% increase in treadmill exercise time for each participant at 1, 3, and 6 months. One individual was unable to walk on treadmill and % increase in walking distance on flat was used. Median (IQR)% increase at 1 month, 125 (4–263, $p=0.08$); 3 months, 85 (62–360, $p=0.015$); and 6 months, 163 (61–425, $p=0.0007$). (U tests.)

Discussion

Meticulous blood-sugar control delays the onset of or prevents diabetic neuropathy,^{1,14} and ameliorates symptoms in those with acute painful neuropathy.¹⁵ However, excellent glycaemic control may be beyond the capability of some patients with type II diabetes who often present with neuropathy when metabolic control seems satisfactory. Although the first step in painful neuropathy should be to improve glycaemic control, additional drug treatment is usually required.⁸ Tricyclic compounds are the most effective but many patients fail to respond and side-effects are frequent. Other drugs include anticonvulsants, mexiletine, intravenous lignocaine, and topical capsaicin.⁸ Our finding of pain relief with implantable ESCS in these patients without the need for drugs is an improvement in management.

Several studies have demonstrated the safety and effectiveness of ESCS for the treatment of chronic pain but no studies have looked at chronic diabetic neuropathic pain. Patients' selection is obviously important and we were careful to assess both the presence and severity of neuropathy. Psychological assessment of patients is also essential because ESCS seems to be more effective in those without major psychological overlay.^{16,17} The best results from ESCS would be expected in those with well-localised pain, and in those whose area of pain is covered fully with induced paraesthesiae.¹⁸

Our results demonstrate that ESCS was effective in the treatment of chronic diabetic neuropathic pain, improving both background and peak pain, and answers on the McGill pain questionnaire, throughout the study. The number of patients we studied was small. We had a placebo "stimulator" in the initial trial phase, but it was not possible to blind the study when patients got used to the quality of the stimulus received, after implantation of the X-Trel receiver. Although fully blind studies are impossible, a placebo response is unlikely because of sustained benefit in some patients.^{9,19} Also the need for accurate positioning of the electrode above the level of pain and with the projection of paraesthesiae over the whole area of pain to achieve pain relief, and the observation that pain relief is lost immediately when there is lead displacement argues against a placebo response.^{9,19}

In addition to spontaneous dysaesthetic pain, all our patients had unpleasant sensory symptoms on walking ("walking barefoot on pebbles), and half the patients could only manage 30 seconds or less on a treadmill. The worst-affected patients were more or less confined to home, unable to cope even with, for instance, shopping, while others could not do gardening, or dancing. All the patients had an increased exercise threshold, with a median increase of over 150% at 6 months. One teacher could even continue full-time work.

Peripheral nerves in diabetic neuropathy have impaired blood flow.^{20,21} Because ESCS improves microvascular blood flow in severe limb ischaemia,²² we speculate that the improvement in pain scores when the stimulator is turned on may in part be due to improvement in nerve blood flow. ESCS is thought to stimulate the dorsal columns (ie, A-beta fibres) inhibiting the C fibres in some manner, and thus interrupting/gating pain input.²³ With loss or gross dysfunction of the inhibitory A-beta fibres, ESCS is unlikely to work. This was the case in the two patients who failed to respond to the initial trial stimulation. Elevation of the VPT to the unrecordable range (or complete absence of vibration and joint-position

sense on clinical examination) may characterise patients who are unlikely to respond to ESCS, and may indicate dorsal column damage in diabetic neuropathy.

We have demonstrated that ESCS offers a new and effective treatment for chronic diabetic neuropathic pain in some cases, improves exercise tolerance, and should be considered in patients who do not respond to drug treatment.²⁴

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