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Spinal cord stimulation versus conventional medical management for neuropathic pain: A multicentre randomised controlled trial in patients with failed back surgery syndrome

Krishna Kumar [a,*], Rod S. Taylor [b], Line Jacques [c], Sam Eldabe [d], Mario Meglio [e], Joan Molet [f], Simon Thomson [g], Jim O'Callaghan [h], Elon Eisenberg [i], Germain Milbouw [j], Eric Buchser [k], Gianpaolo Fortini [l], Jonathan Richardson [m], Richard B. North [n]

[a] *Department of Neurosurgery, Regina General Hospital, 1440 14th Avenue, Regina, Sask., Canada S4P OW5*
[b] *Peninsula Medical School, University of Exeter, UK*
[c] *Department of Neurosurgery, Montreal Neurological Institute and Hospital, Montreal, Canada*
[d] *Department of Pain and Anaesthesia, James Cook University Hospital, Middlesbrough, UK*
[e] *Department of Functional Neurosurgery, Gemelli Catholic University Hospital, Rome, Italy*
[f] *Department of Neurosurgery, Santa Creu i Sant Pau Hospital, Barcelona, Spain*
[g] *Pain Clinic, Basildon and Thurrock University Hospitals, Basildon, UK*
[h] *Pain Clinic, Axxon Pain Medicine, Brisbane, Australia*
[i] *Pain Relief Unit, Rambam Medical Center, Haifa, Israel*
[j] *Neurosurgery, Namur Regional Hospital, Namur, Belgium*
[k] *Pain Clinic, Morges Hospital, Morges, Switzerland*
[l] *Pain Clinic, Varese Regional Hospital and Macchi Foundation, Varese, Italy*
[m] *Department of Pain and Anesthesia, Bradford Hospitals, Bradford, UK*
[n] *Department of Neurosurgery, The Johns Hopkins University School of Medicine, Baltimore, MD, USA*

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Abstract

Patients with neuropathic pain secondary to failed back surgery syndrome (FBSS) typically experience persistent pain, disability, and reduced quality of life. We hypothesised that spinal cord stimulation (SCS) is an effective therapy in addition to conventional medical management (CMM) in this patient population. We randomised 100 FBSS patients with predominant leg pain of neuropathic radicular origin to receive spinal cord stimulation plus conventional medical management (SCS group) or conventional medical management alone (CMM group) for at least 6 months. The primary outcome was the proportion of patients achieving 50% or more pain relief in the legs. Secondary outcomes were improvement in back and leg pain, health-related quality of life, functional capacity, use of pain medication and non-drug pain treatment, level of patient satisfaction, and incidence of complications and adverse effects. Crossover after the 6-months visit was permitted, and all patients were followed up to 1 year. In the intention-to-treat analysis at 6 months, 24 SCS patients (48%) and 4 CMM patients (9%) ($p < 0.001$) achieved the primary outcome. Compared with the CMM group, the SCS group experienced improved leg and back pain relief, quality of life, and functional capacity, as well as greater treatment satisfaction ($p \leqslant 0.05$ for all comparisons). Between 6 and 12 months, 5 SCS patients crossed to CMM, and 32 CMM patients crossed to SCS. At 12 months, 27 SCS patients (32%) had experienced device-related complications. In selected patients with FBSS, SCS provides better pain relief and improves health-related quality of life and functional capacity compared with CMM alone.

* Corresponding author. Tel.: +1 306 781 6154; fax: +1 306 781 6153.
E-mail addresses: krishna.kumar@rqhealth.ca, krishnakumar9@hotmail.com (K. Kumar).

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1. Introduction

Neuropathic pain, caused by a primary lesion or dysfunction of the nervous system (Merskey and Bogduk, 1994), has a reported prevalence in a general or primary care population of 1.5–8% (Bennett, 1998; Hall et al., 2006; Torrance et al., 2006), however, neuropathic pain is often under-diagnosed and under-treated (Taylor, 2006). Compared with nociceptive pain, neuropathic pain is more severe, more likely to be chronic, and less responsive to the administration of analgesic drugs and other conventional medical management (Dworkin et al., 2003; Finnerup et al., 2005). The burden of disability associated with neuropathic pain is substantial, as is the cost of treatment. For example, health-related quality of life in patients with neuropathic pain is comparable to that experienced by those with conditions such as cancer or chronic heart failure (Meyer-Rosberg et al., 2001), and an analysis of a large United States insurance database revealed that the healthcare costs of patients with neuropathic pain were threefold those of age- and sex-matched claimants without neuropathic pain (Berger et al., 2004).

The most common location of chronic neuropathic pain is the back and legs (Dworkin et al., 2003), and 10–40% of patients who have undergone lumbosacral spine surgery to alleviate neuropathic radicular pain instead experience persistent or recurrent pain (Wilkinson, 1991; North et al., 1993). In carefully chosen patients with this condition, which is often referred to as "failed back surgery syndrome" (FBSS), spinal cord stimulation (SCS) has been shown to provide effective pain relief (Turner et al., 2004; Taylor et al., 2005; Kumar et al., 2006). A randomised controlled trial by North et al. demonstrated that compared with re-operation, SCS provides effective pain relief for at least 3 years (North et al., 2005). However, non-surgical medical therapy (which can include a spectrum of rehabilitative and drug therapies) is the treatment of choice for the management of such patients (Attal et al., 2006). The relative effectiveness of SCS compared with such conventional non-surgical neuropathic pain management has not been assessed in a randomised controlled trial setting. The PROCESS study is a prospective, randomised, controlled, multicentre trial designed to test the hypothesis that SCS in addition to conventional medical management (CMM) is more effective in FBSS patients than CMM alone (Kumar et al., 2005). We report here efficacy findings at 6-months follow up (the primary analysis point of the trial) and complications and adverse events at 12 months.

2. Methods

The Prospective Randomised Controlled Multicentre Trial of the Effectiveness of Spinal Cord Stimulation (PROCESS, ISRCTN 77527324) recruited 100 patients in a total of 12 centres in Europe, Canada, Australia, and Israel between April 2003 and June 2005. The Institutional Review Board or Ethics Committee at each site approved the protocol. All patients gave informed consent before commencement of treatment.

2.1. Patients

Eligible patients were at least 18 years of age. They suffered from neuropathic pain of radicular origin (radiating in dermatomal segments L4 and/or L5 and/or S1) predominantly in the legs (exceeding back pain), of an intensity of at least 50 mm on a visual analogue scale (VAS: 0 equalling no pain, to 100 mm representing the worst possible pain) for at least 6 months after a minimum of one anatomically successful surgery for a herniated disc. Thus all patients had a documented history of nerve injury, i.e. root compression by herniated disc, competent to explain the complaint of radiating pain. In addition the neuropathic nature of pain was checked as per routine practice at the centre (i.e. by clinical investigation of pain distribution, examination of sensory/motor/reflex change, with supporting tests such as X-ray, MRI and EMG). Some of the eligible patients had undergone additional procedures, namely repeat lumbar disc operations, laminectomies with or without foraminotomies or spinal fusion.

Patients were excluded if they had another clinically significant or disabling chronic pain condition; an expected inability to receive or operate the SCS system; a history of a coagulation disorder, lupus erythematosus, diabetic neuropathy, rheumatoid arthritis, or ankylosing spondylitis; evidence of an active psychiatric disorder, another condition known to affect the perception of pain, or inability to evaluate treatment outcome as determined by the principal investigator; life expectancy of less than 1 year; or an existing or planned pregnancy.

2.2. Procedure

Eligible patients were randomly assigned in a 1:1 ratio to conventional medical management with SCS (SCS group) or without SCS (CMM group). A biostatistician prepared random computer-generated blocks (random sequence of either 2 or 4 patients) on a per site basis. The randomisation was electronically locked and could only be accessed after a patient entered the trial. Given the nature of the intervention, it was impossible to blind patients and difficult to blind investigators during the trial.

All patients assigned to the SCS group underwent a screening trial. Those experiencing at least 80% overlap of their pain with stimulation-induced paresthesia and at least 50% leg pain relief received an implantable neurostimulation system (Synergy™ system, Medtronic, Inc., Minneapolis, MN). Details

of the implantation procedure have been described elsewhere (Barolat and North, 2002). All patients were followed for 12 months whether or not they received an implant.

At baseline, the non-SCS therapy received by both groups was reviewed and actively managed, at the discretion of the study investigator and according to local clinical practice. Non-SCS therapy included oral medications (i.e. opioid, non-steroidal anti-inflammatory drug, antidepressant, anticonvulsant/antiepileptic and other analgesic therapies), nerve blocks, epidural corticosteroids, physical and psychological rehabilitative therapy, and/or chiropractic care. The protocol excluded other invasive therapy, such as spinal surgery or implantation of an intrathecal drug delivery system.

The primary outcome was the proportion of patients achieving at least 50% leg pain relief at 6 months. Secondary outcomes were improvement in back and leg pain, health-related quality of life, and functional capacity; change in the use of pain medication and non-drug pain therapy; patient satisfaction with treatment; and incidence of adverse effects.

Baseline data on age, sex, employment status, legal actions related to FBSS, prior back operations, and source of major pain were collected for all patients. Outcome measures were assessed prior to randomisation (baseline) and at 1, 3, 6, 9, and 12 months after initiation of treatment. After 6 months, patients failing to achieve adequate pain relief could request crossover to the alternative treatment, which occurred upon physician approval. Patients who crossed from SCS to CMM had their SCS systems explanted or switched off.

We used patient self-completed questionnaires. During four days preceding a study visit, pain intensity was assessed by the patient in a "pain diary" (recording the VAS three times per day separately for back and leg pain). Pain data were expressed as absolute values and as the proportion of patients who achieved 30%, 50%, 80%, or more pain relief at follow up (European Medicines Agency Committee, 2006). We used the Short-Form 36 (SF-36) questionnaire to assess quality of life (McHorney et al., 1993) and the Oswestry Disability Index version 2 (ODI) to assess functional capacity (Fairbank and Pynsent, 2000). The use of pain medication and non-drug pain therapy, number of patients taking any medication, and daily dose of opioids were also recorded. All opioid doses were converted to a morphine equivalent dose using routine conversion tables (Twycross et al., 2002; Sweetman, 2005). For some drugs, a range was provided; therefore, "low" and "high" morphine equivalent scores were calculated. In addition, the questionnaires assessed employment status and patient satisfaction with treatment ("are you satisfied with the pain relief provided by your treatment?" and "based on your experience so far, would you have agreed to this treatment?"). The nature and frequency of adverse treatment-related events and complications were documented, and the Adverse Events Committee adjudicated all events. Stimulation parameters were also collected (Appendix A).

2.3. Statistical analysis

Based on a previous trial (North et al., 2005), it was assumed that 42.5% of patients in the SCS group would achieve the primary outcome versus 14.5% of patients in the CMM group. Thus groups of 40 patients each would reveal a difference with a power of 80% and a two-tailed alpha of 0.05. Taking into account an attrition rate of 20%, the minimum number of patients required was 100.

As pre-specified, the primary (between group) analysis of all outcomes was performed at 6-months follow up and according to the intention-to-treat (ITT) principle. Additionally a secondary analysis of the primary outcome was conducted at 12-months follow up using both as-treated (outcomes assessed according to treatment received at last visit) and ITT analyses (Kumar et al., 2005). The detailed 12-months outcome report will be described in a separate paper.

The baseline characteristics of the two groups were compared using chi-square and independent t-tests. Between-group comparisons at follow up were made using regression analysis (linear regression for continuous variables, logistic regression for dichotomous variables); with as candidate covariates gender, age at randomisation, time since FBSS surgery, number of spinal surgeries and leg pain location. Baseline characteristics having prognostic value ($p < 0.10$) were entered into a multivariate model, with insignificant effects removed in a stepwise manner. We expressed binary outcomes as risk differences and odds ratios and continuous outcomes as mean differences. The sensitivity analysis of the effect of missing outcome values used the "last observation carried forward" method. The imputed and non-imputed results did not differ. Interaction terms were used to undertake two exploratory subgroup analyses on the primary outcome, the number of previous back surgeries (<3 vs. $\geqslant 3$) and duration of diagnosis of FBSS (<12 vs. $\geqslant 12$ months). Inferential testing was undertaken at 6- and 12-months follow up. To allow for the multiplicity of analyses, two-tailed p-values less than 0.01 are considered to indicate statistical significance for within- and between-group comparisons, and results are expressed as 99% confidence intervals.

Complications and adverse events in both groups at 12 months are reported descriptively (Kumar et al., 2005; International Committee on Harmonisation, 2006). All statistical analyses were conducted using SAS version 9.1.3 software (SAS Institute, Cary, NC).

3. Results

3.1. Study population

Of 214 consecutive patients with FBSS who sought treatment during the enrolment period, 135 (63%) were eligible to participate. The primary reason for exclusion was predominant back pain (51 patients, 24%) (Fig. 1). Of the eligible patients, 100 (74%) consented to randomisation. The age (mean 49 years, standard deviation 11, $p = 0.64$) and sex distribution (43% male, $p = 0.43$) of patients who did not consent were similar to those who did. Of the 100 randomised patients, 52 were assigned to the SCS group and 48 to the CMM group. Baseline characteristics were relatively well balanced in the two groups, the only exception being a slightly higher back pain score in the CMM group (Table 1, see also Appendix B, Supplementary data). Although a low proportion of patients were receiving non-drug

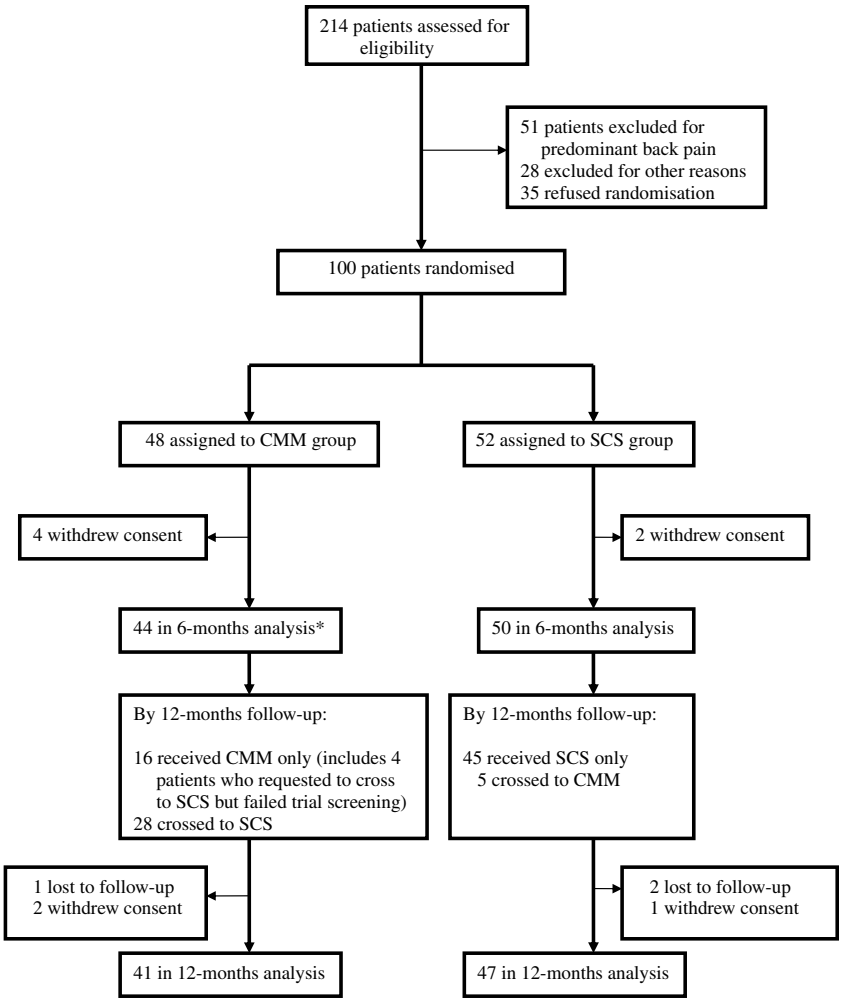


Fig. 1. Trial profile. Out of 214 patients assessed, 100 patients were randomised to CMM ($n = 48$) or SCS ($n = 52$). At 6 months, respectively, 44 and 50 patients remained in each group. *1 patient failed to provide primary outcome data at 6-months visit.

treatment (such as physical rehabilitation) at baseline, many of these treatments had been tried in the past.

Of the 52 patients randomised to the SCS group, nine failed to achieve 50% or more leg pain relief or 80% paresthesia coverage during the screening trial. Five of these patients requested that they be implanted with a device, therefore 48 patients received the Synergy™ system (Medtronic Inc.).

Two patients in the SCS group and four in the CMM group had their treatment terminated before the 6-months follow up due to withdrawal of consent. In the CMM group, one patient did not complete the pain diary at the 6-months visit. Primary outcome data were therefore available for 93 patients (50 SCS group and 43 CMM group) at 6 months. After 6 months, five patients (10%) in the SCS group crossed to CMM: four of these

Table 1
Baseline characteristics

	CMM group ($n = 48$)	SCS group ($n = 52$)	Between-group difference p-value
Sex male – n (%)	21 (44)	30 (58)	0.23
Age in years – mean (SD)	52.0 (10.7)	48.9 (10)	0.15
Time since last surgery – years (SD)	4.6 (4.3)	4.7 (5.1)	0.93
>1 surgery – n (%)	22 (46)	28 (54)	0.55
Currently employed – n (%)	10 (21)	12 (23)	0.81
History of legal action related to back pain – n (%)	8 (17)	5 (10)	0.38
Unilateral leg pain – n (%)	32 (67)	33 (63)	0.83
Bilateral leg pain – n (%)	16 (33)	19 (37)	
Back pain VAS – mean (SD)	44.8 (23.2)	54.5 (24.3)	0.03
Leg pain VAS – mean (SD)	73.4 (14.0)	76.0 (13.0)	0.35

due to insufficient pain relief (<50%) with SCS and one patient following an "allergic reaction". In contrast, 32 patients (73%) in the CMM group crossed to SCS; the majority due to insufficient pain relief but one patient due to dissatisfaction with treatment. Four of CMM patients who elected to cross to SCS failed the screening trial stimulation; therefore, 28 patients randomised to CMM received an implantable SCS system after the 6-months visit. All received the Synergy™ system (Medtronic Inc.) except for three patients whose body type required a small implantable pulse generator and received the Itrel®3 system (Medtronic Inc.).

3.2. Primary outcome at 6 months

Twenty-four patients in the SCS group (48%) and four patients in the CMM group (9%) achieved the primary outcome of 50% leg pain relief ($p < 0.001$) (Table 2a). The pattern of primary outcome differences between the two groups at 1 and 3 months was similar to 6-months outcomes (Fig. 2).

A sensitivity analysis excluding the five patients in the SCS group who did not meet the screening criteria but requested an implant revealed that their exclusion would not affect the group outcome (51% vs. 9%, $p < 0.001$). In a worst-case analysis, which assumed that patients unavailable for 6-months follow up in the CMM group achieved the primary outcome but those in the SCS group did not, SCS remained more effective (46% vs. 17%, $p = 0.002$).

Exploratory subgroup analyses of patients with either less than three back surgeries or a diagnosis of FBSS of less than 12-months duration indicated a trend that these patients were more likely to achieve the primary outcome with SCS than their counterparts; however, the interaction terms for these subgroups were not significant (number of back surgeries, $p = 0.95$; duration of FBSS, $p = 0.20$). These subgroup analyses should be regarded as hypothesis generating.

3.3. Secondary outcomes at 6 months

Compared with the CMM group, SCS group patients experienced lower levels of back pain ($p = 0.008$) and leg pain ($p < 0.0001$), enhanced health-related quality of life on seven of the eight dimensions of the SF-36 ($p \leqslant 0.02$), superior function (ODI, $p < 0.001$), and greater treatment satisfaction ($p < 0.001$) (Table 2b). The SCS group exhibited a trend towards a decrease in both analgesic drug intake (as assessed by morphine equivalency and the proportion of patients using medication) and in non-drug therapy use ($0.21 \geqslant p \geqslant 0.02$). A total of 9 patients ceased opioids at follow up, 8 SCS patients and 1 CMM patient. Rates of return to work did not differ between the groups ($p = 0.36$). The pattern of secondary outcome differences between groups at 6 months was similar to that at 1 and 3 months (Fig. 2).

3.4. Primary outcome at 12 months

According to per treatment analysis, the primary outcome was achieved in 48% of the 71 patients implanted with a stimulator and 18% of the 17 patients receiving conventional medical therapy alone ($p = 0.03$). To quantify the impact of crossovers, we undertook a *post hoc* modified ITT analysis where patients who crossed over at 6 months were categorized as primary outcome failures according to their initial random allocation (North et al., 2005). In this analysis, 34% of the SCS group and 7% of the CMM group achieved the primary outcome ($p = 0.005$). Detailed 12-months results will be described in a different paper.

3.5. Complications and adverse events at 12 months

Of 84 patients who received an electrode (either during the screening trial or as a result of system implantation) during the 12 months of the study, 27 (32%) experienced a total of 40 device-related complications. For 20 patients (24%), surgery was required to resolve the event (Table 3a). Principal complications were electrode migration (10%), infection or wound breakdown (8%), and loss of paresthesia (7%). In total, 18 (35%) of the SCS group and 25 (52%) of the CMM group experienced one or more non-device-related events, most commonly a drug adverse event or development of a new illness, injury, or condition (Table 3b).

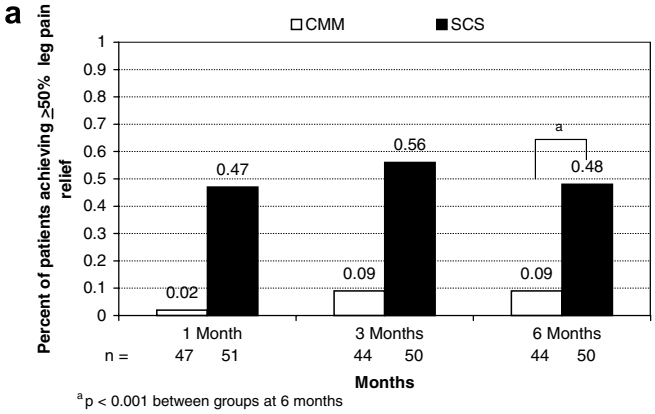
4. Discussion

This international multicentre prospective randomised controlled trial shows that SCS provides pain relief and improves health-related quality of life and functional capacity in patients with neuropathic pain secondary to FBSS. In contrast, CMM alone provided little or no pain relief or other outcome benefit.

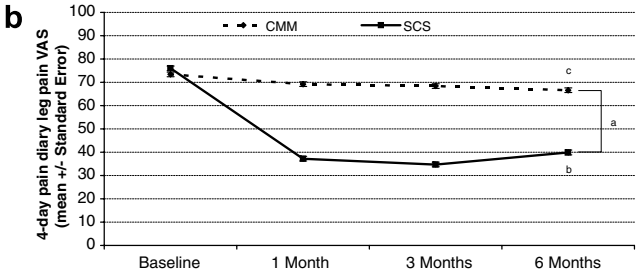
Table 2a
Primary outcome measure at 6 months

	CMM group ($n = 44$)	SCS group ($n = 50$)	Between-group risk difference (99% CI)	Odds ratio (99% CI)	Between-group difference p-value*
⩾50% leg pain relief – n (%)	4 (9%)	24 (48%)	39% (18–60%)	9.23 (1.99–42.84)	<0.001

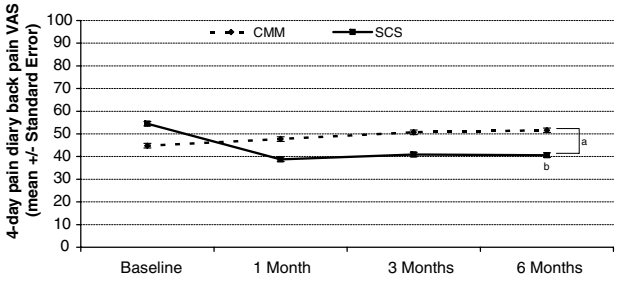
* Adjusted for location of leg pain and therefore p-values may not exactly correspond to the unadjusted confidence intervals.



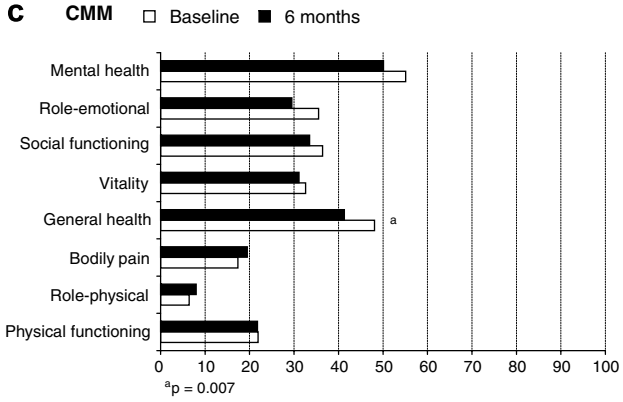
[a] p < 0.001 between groups at 6 months



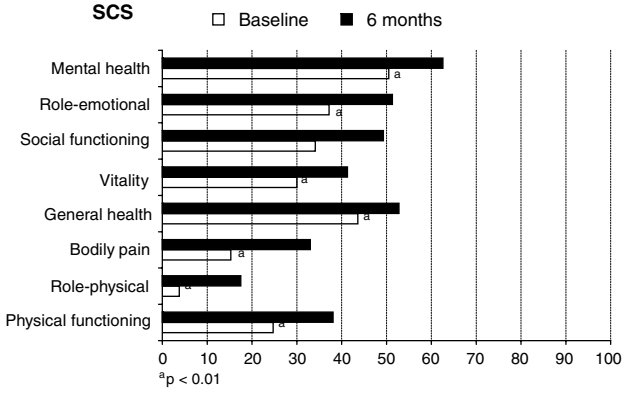
[a] p < 0.001 between groups at 6 months
[b] p < 0.001 in SCS group between 6 months and baseline
[c] p = 0.03 in CMM group between 6 months and baseline



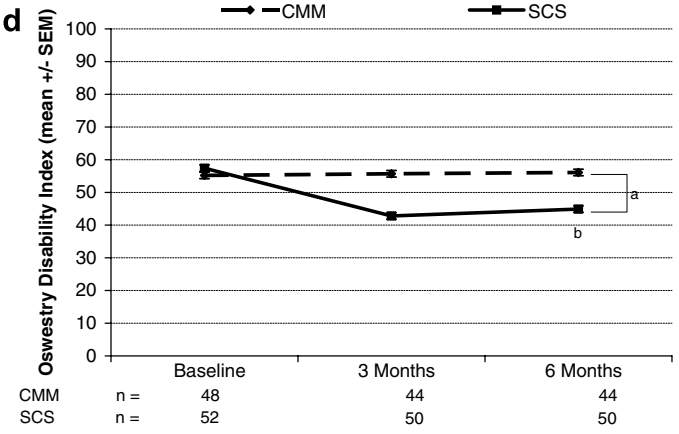
[a] p = 0.008 between groups at 6 months
[b] p = 0.007 in SCS group between 6 months and baseline



[a] p = 0.007



[a] p < 0.01



[a] p = 0.0002 between groups at 6 months
[b] p < 0.0001 in SCS group between 6 months and baseline

Table 2b
Secondary outcome measures at 6 months

	CMM group ($n = 44$)	Within group difference p-value*	SCS group ($n = 50$)	Within group difference p-value*	Between-group risk difference or difference in means (99% CI)	Odds ratio (99% CI)	Between-group difference p-value**
Leg pain relief ($\geqslant 30\%$) – n (%)	8 (18%)		32 (64%)		46% (23 to 69%)	8.00 (2.27 to 28.22)	<0.0001
Leg pain relief ($\geqslant 80\%$) – n (%)	3 (7%)		11 (22%)		15% (−3 to 33%)	3.85 (0.65 to 22.71)	0.05
Back pain VAS – mean (SD)	51.6 (26.7)	0.10	40.6 (24.9)	0.007	−11.0 (−25.0 to 3.0)		0.008
Leg pain VAS – mean (SD)	66.6 (24.0)	0.03	39.9 (26.3)	<0.0001	−26.7 (−40.4 to −13.0)		<0.0001
Short-Form 36 – mean (SD)							
Physical function	21.8 (16.2)	0.67	38.1 (23.0)	<0.001	16.3 (5.3 to 27.2)		<0.001
Role-physical	8.0 (22.7)	0.67	17.5 (32.4)	0.006	9.5 (−5.9 to 24.9)		0.12
Bodily pain	19.5 (12.9)	0.12	33.0 (20.9)	<0.001	13.4 (3.9 to 23.0)		<0.001
General health	41.3 (24.4)	0.007	52.8 (22.3)	0.004	11.5 (−1.2 to 24.1)		<0.001
Vitality	31.1 (20.9)	0.97	41.3 (21.5)	0.002	10.2 (−1.4 to 21.7)		0.01
Social functioning	33.5 (18.4)	0.65	49.3 (29.7)	0.001	15.7 (2.1 to 29.4)		0.002
Role-emotional	29.5 (40.8)	0.31	51.3 (44.3)	0.09	21.8 (−1.4 to 45.0)		0.02
Mental health	50.1 (23.3)	0.16	62.6 (22.2)	0.004	12.5 (0.1 to 24.8)		0.002
Oswestry disability index – mean (SD)	56.1 (17.9)	0.85	44.9 (18.8)	<0.001	−11.2 (−21.2 to −1.3)		<0.001
Morphine (oral equivalent daily mg) – mean (SD)							
Low	96.9 (214)	0.19	68.3 (139)	0.89	−28.6 (−125.5 to 68.3)		0.21
High	125 (281)	0.23	76.8 (146)	0.92	−48.4 (−167.8 to 71.1)		0.20
Drug therapy – n (%)							
Opioids	31 (70%)	0.13	28 (56%)	0.11	−15% (−40 to 11%)	0.53 (0.17 to 1.64)	0.20
NSAIDs	22 (50%)	1.00	17 (34%)	0.58	−16% (−42 to 10%)	0.52 (0.17 to 1.54)	0.14
Antidepressants	24 (55%)	0.69	17 (34%)	0.63	−21% (−47 to 5%)	0.43 (0.14 to 1.28)	0.06
Anticonvulsants	22 (50%)	0.06	13 (26%)	0.18	−35% (−49 to 1%)	0.35 (0.11 to 1.10)	0.02
Main non-drug therapy – n (%)							
Physical rehabilitation	8 (18%)	0.02	3 (6%)	0.63	−12% (−30 to 5%)	0.29 (0.05 to 1.80)	0.11
Psychological rehabilitation	5 (11%)	0.25	1 (2%)	1.00	−9% (−23 to 4%)	0.16 (0.01 to 2.82)	0.09
Acupuncture	3 (7%)	0.50	0	***	−7% (−17 to 3%)	***	0.10
Massage	4 (9%)	0.63	0	***	−9% (−20 to 2%)	***	0.05
TENS	5 (11%)	1.00	0	***	−11% (−24 to 1%)	***	0.02
Patient satisfaction – n (%)							
Satisfied with pain relief	8 (18%)		33 (66%)		48% (25 to 71%)	8.73 (2.46 to 31.01)	<0.001
Agree with treatment	22 (50%)		43 (86%)		36% (13 to 59%)	6.14 (1.66 to 22.67)	<0.001
Return to work – n (%)+	1/33 (3%)		4/36 (11%)		8% (−7 to 22%)	4.00 (0.21 to 76.18)	0.36

*: Compared with baseline; **: adjusted for baseline values and covariates (selected from gender, age at randomisation, time since FBSS surgery, number of spinal surgeries and leg pain location) and therefore p-values may not exactly correspond to the unadjusted confidence intervals; +: based on number of individuals not working at baseline; TENS: transcutaneous nerve stimulation; NSAID: non-steroidal anti-inflammatory drug; SD: standard deviation; VAS: visual analogue scale; ***: odds ratio or p-value not calculable due to zero events.

The favourable effect of SCS on neuropathic pain is consistent with the results of previously reported trials. A randomised controlled trial by North et al. concluded that SCS was more effective than re-operation as a treatment for persistent, primarily radicular, pain after lumbosacral spine surgery (North et al., 2005). Kemler et al.

Fig. 2. (a) Primary endpoint: proportion of patient achieving $\geqslant 50\%$ leg pain relief. In an ITT analysis at 6 months, significantly more patients in the SCS group (48%) experienced $\geqslant 50\%$ reduction of their VAS leg pain score compared with the CMM group (9%). Inferential testing was only performed at 6 months. (b) Leg and back VAS pain scores at baseline, 1, 3 and 6 months. In an ITT analysis at 6 months, CMM patients showed a significant reduction from baseline in the leg pain score only, whereas the SCS group reported a significant reduction in both back and leg pain scores. At 6 months, the SCS group showed significantly greater reduction in back ($p = 0.008$) and leg ($p < 0.001$) pain scores compared with CMM. Inferential testing was only performed at 6 months. (VAS, visual analogue scale). (c) Short-Form 36 scores at baseline and 6 months: In an ITT analysis at 6 months, health-related quality of life in the CMM group significantly improved in only 1 domain out of 8 compared with baseline. In the SCS group, quality of life significantly improved in 7 out of 8 domains. When comparing the changes between the 2 groups at 6 months, there was a significant difference in 7 out of 8 domains (except role-physical) in favour of SCS ($p < 0.02$). The SF-36 questionnaire was not completed at the 1-month visit. Results at 3 months were similar to those at 6 months. (d) Oswestry Disability Index score at baseline, 3, and 6 months: In an ITT analysis at 6 months, only the SCS group showed a significant improvement in function compared with baseline. Patients in the SCS group showed a significantly greater improvement in function (showed by a reduction in the disability score) compared with CMM patients ($p = 0.0002$). The Oswestry questionnaire was not completed at the 1-month visit. Inferential testing was only performed at 6 months.

Table 3a
SCS-related complications at 12 months

Event etiology	Number of events	Patients with ⩾1 event ($n = 84$)	Patients requiring surgery ($n = 84$)
Total hardware related	13	11 (13%)	10 (12%)
Lead migration	10	8 (10%)	8 (10%)
Lead/extension fracture/torqued contacts	2	2 (2%)	1 (1%)
IPG migration	1	1 (1%)	1 (1%)
Loss of therapeutic effect, loss of paresthesia, or unpleasant paresthesia	6	6 (7%)	1 (1%)
Technique[a]	5	4 (5%)	4 (5%)
Total biological	16	16 (19%)	6 (7%)
Infection/wound breakdown	7	7 (8%)	5 (6%)
Pain at IPG/incision site	5	5 (6%)	1 (1%)
Neurostimulator pocket – fluid collection	4	4 (5%)	0 (0%)

IPG: implantable pulse generator; CSF: cerebrospinal fluid.
[a] (1) Cap not installed on IPG when only one lead was implanted: (2) suboptimal connection of extension to IPG led to intermittent stimulation; (3) anteriorly implanted electrode caused shocks; (4) lead cut during implant; (5) dural tear during implant.

reported a significant reduction in pain in patients with complex regional pain syndrome patients randomised to SCS with physical therapy compared with physical therapy alone (Kemler et al., 2006). Tesfaye et al. found a significant improvement in pain relief in the SCS treated diabetic neuropathic pain patients compared to sham stimulation (Tesfaye et al., 1996). Future studies of the differential effects of SCS on various types of neuropathic pain (e.g. ongoing paroxysmal allodynia) might contribute to a better understanding of pain pathophysiology and SCS mechanisms.

Our finding that SCS enhanced health-related quality of life was key, given that quality of life has previously been shown to be severely compromised in patients with chronic pain (Samsa et al., 1999; Galvez et al., 2006).

Table 3b
Adverse events by group at 12 months

	CMM group n (%)	SCS group n (%)
Number	48	52
Patients with ⩾1 non-SCS related event	25 (52%)	18 (35%)
Non-SCS events	37	25
Patients with ⩾1 drug adverse event	10 (21%)	2 (4%)
Drug adverse events	12	2
Patients with ⩾1 event of extra pain	2 (4%)	0 (0%)
Events of extra pain	2	0
Patients with ⩾1 new illness/injury/condition	11 (23%)	13 (25%)
Events of new illness/injury/condition	13[a]	16
Patients with ⩾1 worsening of pre-existing condition	7 (15%)	7 (13%)
Events of worsening of pre-existing condition	10[b]	7

[a] Includes 1 patient who required a back reoperation between the 6- and 12-months visits.
[b] Includes 1 patient who required a back reoperation between the 6- and 12-months visits.

Compared with CMM, treatment with SCS resulted in greater improvement in all SF-36 domains. A difference of 3–5 points is considered clinically relevant (Haythornthwaite and Benrud-Larson, 2000), and between-group differences of 9.5–21.8 points were observed in this study. These results are also noteworthy since they are reported at 6 months, which compares favourably with the duration of studies of pharmacological treatment of neuropathic pain (typically ranging from 3 to 12 weeks) (Finnerup et al., 2005).

Several studies have shown that SCS is a safe procedure with a reported risk of generally minor and correctable complications in 20–75% of patients (Cameron, 2004; Turner et al., 2004; Kumar et al., 2006). The overall risk of a device-related complication in the first year after implantation in this trial (32%) is at the low end of this range. A recent review of safety outcomes found that electrode migration (incidence of 15.1%) and infection (incidence of 3.4%) were the two most frequently reported complications of SCS (Cameron, 2004). The corresponding incidences in the PROCESS study were 10% (8 patients) electrode migration and 8% (7 patients) infection. A partial explanation of this apparently high rate of infection is that of two infections occurring during the screening trial; such infections might not have been reported in previous studies. We propose that future neuromodulation studies consistently collect and report safety outcomes as we have in this trial.

This study has several strengths. First, it is the largest trial of SCS for the management of neuropathic pain. Second, the primary endpoint of 50% or more pain relief is considerably in excess of the licensing threshold of 30% recommended by the European Medicines Evaluation Agency (European Medicines Evaluation Agency, 2006). Furthermore, the ITT analysis showed significant improvement in this primary endpoint at 6 months in the SCS group, even though 10% of these patients failed the screening trial and had no device implanted. Finally,

the study had a pragmatic design – in particular, the nature and intensity of control care (CMM) was at the discretion of treating physicians, and minimal patient exclusions were employed. This mirrors clinical practice, enabling greater generalization of the results, while controlling for potentially confounding variables through randomisation (Tunis et al., 2003; Hartling et al., 2005).

Potential limitations of this trial included the lack of blinding or independent assessment, and, for the post-6-months data, the treatment crossovers. The 6-months comparison endpoint was chosen as the longest that patients could reasonably and ethically be asked to wait before being given the option of crossover; however, data were collected on complications and outcomes beyond 6 months. The high number of crossovers compromises the ability to make an unbiased assessment of the effectiveness of SCS beyond 6 months because the prognostic case mix of crossovers might not reflect that of the patients who remained in the randomised group. Also, compared with those who remained in their randomised group, the outcomes for crossovers might have been influenced by the therapy received initially and a different exposure time on the alternate therapy. To best reflect treatment differences at 12 months, we undertook a *post hoc* analysis where patient crossover was assumed to represent a failure to achieve the primary outcome. This analysis showed the continued effectiveness of SCS compared with control. This supports the findings of meta-analyses of uncontrolled studies in over 3000 neuropathic back and leg pain patients, which indicate that SCS can provide effective pain relief up to 10 years post-implantation (Turner et al., 2004; Taylor et al., 2005).

The possibility of crossover might have biased ('expectation bias') the outcome in the CMM group. The expectations of the patients not randomised to SCS primarily to crossover to the potentially more effective treatment after 6 months might have penalised the CMM. This effect could be only controlled for by a true crossover or parallel group blinded study design, neither of which was feasible or practical.

Although blinding would minimize the risk of a placebo effect, it is both ethically and methodologically challenging in the field of medical device evaluation. Because of the paresthesia that accompanies stimulation, it is difficult to blind SCS. Also, the fact that we observed a similar level of pain relief in the SCS patients at 1, 3 and 6 months reduces likelihood that our results reflect solely a placebo effect (Kemler et al., 2000).

The lack of outcome assessment by an independent third party can be a potential source of assessment bias. However, given that trial primary outcome and majority of secondary outcomes were based on questionnaires completed by the patients, the risk of such bias in this case was likely to be small.

Recent systematic reviews have reported that a minority of neuropathic pain patients obtain 50% or more pain relief with conventional pharmacologic management, a proportion of which experience significant side effects (Finnerup et al., 2005; Attal et al., 2006; Eriksen et al., 2006). Despite the fact that a 6-months follow up offers only a short period in which to wean patients from opioid medication (a process that can take many months), our results show a trend towards opioid reduction or cessation in the SCS patients. Given the moderate success and accepted risk of harm with conventional drug therapies, the outcomes of the PROCESS trial are especially significant for the management of patients with neuropathic pain related to FBSS.

5. Conclusions

Compared with CMM alone, SCS improves pain relief, quality of life, functional capacity and patient satisfaction in selected patients with neuropathic pain related to FBSS.

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Appendix A. SCS stimulation parameters

Forty-three patients had available reprogramming data at 6 months. Their mean (standard deviation) settings were an amplitude of 3.7 V (2.0), a pulse width of 350 μs (95.5) and a rate of 49 Hz (16.4). Almost half (45%) the patients required an amplitude of 4 V or more.

Appendix B and C. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.pain.2007.07.028.

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