Spinal Cord Stimulation (Neurostimulation): An Accelerated Systematic Review

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Spinal cord stimulation (neurostimulation):
an accelerated systematic review

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The Executive of the Council of the Royal Australasian College of Surgeons in February 2004
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Summary

Background
Spinal cord stimulation (SCS) is used to treat chronic intractable pain, mostly of the trunk or the extremities, but it is also used to treat anginal pain. SCS is thought to work by stimulating nerve fibres in the spinal cord, which inhibits pain signals to the brain.

Objective
To assess the effectiveness and safety of SCS by accelerated systematic review.

Methods
MEDLINE and PREMEDLINE were searched up to April 2003 and The Cochrane Library Issue 2, 2003 was searched for reports of randomised controlled trials (RCTs) comparing SCS with an alternative treatment, placebo or no treatment. RCTs were included if they reported pain or pain relief as an outcome.

Results
Nine RCTs of SCS covering five indications were included – four angina trials, one failed back surgery syndrome, two critical limb ischaemia, one complex regional pain syndrome, and one painful diabetic neuropathy. SCS was more effective in terms of pain relief or reducing anginal attacks when compared with placebo or delayed implantation, but no difference was seen in the comparisons with CABG or switching SCS on and off in the same patient. For critical limb ischaemia, SCS was more effective in relieving pain than analgesia alone, but no difference was seen when SCS plus best medical treatment was compared with best medical treatment alone. For complex regional pain syndrome, SCS was more effective in relieving pain than physiotherapy, but no difference was seen between SCS and placebo for painful diabetic neuropathy. Most reported complications were electrode or lead displacements, which required reintervention and repositioning, although these complications are decreasing as the technology improves. A small number of implant and battery failures have been noted, as has one duodenal perforation and two dural punctures. Infection at the implant site seems to be relatively common.

Conclusions
SCS was shown to be effective in relieving pain in only some of the included studies, but the small patient numbers may have limited the ability of studies to detect clinically important differences. SCS appears to be relatively safe, although the long-term safety and effectiveness of SCS have not yet been evaluated.
1. Introduction

Background

Spinal cord stimulation (SCS) or neurostimulation has been used to treat chronic pain for over 30 years. SCS is thought to relieve chronic intractable pain by stimulating nerve fibres in the spinal cord. The resulting impulses in the fibres may inhibit the conduction of pain signals to the brain, according to the pain gate theory proposed by Melzack and Wall in 1965 (Stocks and Williams, 2001) and the sensation of pain is thus blocked. SCS may reduce pain but will not eliminate it – SCS masks the sensation of pain by producing tingling sensations or numbness (paraesthesias) (Alfano et al. undated). After a period of concern about safety and efficacy, SCS is now regaining popularity amongst pain specialists for treating chronic pain (Segal et al. 1999).

Patients with anginal pain have also used SCS. SCS is thought to have an anti-ischaemic effect, increasing myocardial blood flow which results in improved myocardial oxygen supply (Hautvast et al. 1998).

SCS has also been used to treat spasticity but results have been disappointing. In a small RCT of eight moderately disabled children with cerebral palsy, only one continued to use the stimulator on a regular basis, with minimal benefit (Hugenholtz et al. 1988).

SCS is usually considered after treatments such as oral analgesia, physiotherapy, psychological therapy, TENS (transcutaneous electrical nerve stimulation), nerve blocks or corrective surgery have been attempted. One advantage of SCS is its reversibility. Treatment alternatives for managing chronic pain can be represented as a continuum (adapted from Alfano et al. undated):

oral medications, active physical rehabilitation, psychological therapy
↓
corrective surgery
↓
therapeutic nerve blocks
↓
oral opiates
↓
ADVANCED PAIN THERAPIES
spinal cord stimulation
intrathecal drug infusion
↓
neuroablation
The Technique

The spinal cord stimulation technology consists of:

- A lead which delivers electrical stimulation to the spinal cord
- An extension wire which conducts electrical stimulation from the power source to the lead
- A power source which generates the electrical stimulation

In one type of SCS system the power source (a battery) is surgically implanted. In the other type of system, a radio-frequency receiver is implanted, and the power source is worn externally with an antenna over the receiver (Alfano et al. undated). The device can be implanted by laminectomy or percutaneously, but standard modern practice is to trial the SCS device percutaneously. Only those patients achieving significant pain relief from the percutaneous trial are implanted with permanent SCS devices (Furlan et al. 2003).

Paraesthesia distribution is determined by the position of the electrodes (cathodes and anodes) over the spinal cord. While electrodes with multiple contacts make SCS more effective by improving paraesthesia coverage, this increases the potential electrode combinations – for instance there are 6050 possible bipolar combinations for an array of eight contacts (North et al. 2003b). This has been done manually for each combination which is very time-consuming for clinicians and patients, but a computerized interactive method has been developed which enables the patient to work through a prespecified sequence of settings (North et al. 2003b).

SCS systems may be affected by or adversely affect cardiac pacemakers, cardioverter defibrillators, external defibrillators, magnetic resonance imaging (MRI), diathermy, ultrasonic equipment, electrocautery, radiation therapy, theft detectors, security systems and aircraft communications systems (Alfano et al. undated).

Simpson has estimated that 5000 SCS units were implanted in European patients in 1997 (Simpson 1997).

Patient Group

SCS is indicated for patients suffering from chronic intractable pain of the trunk or limbs and is most effective for treating neuropathic pain, which results from actual damage to the peripheral nerves (peripheral deafferentation). It is generally not effective for treating nociceptive pain which results from nerve irritation rather than nerve damage, and can be described as pain signalling actual or impending damage to tissues, muscle, fascia, ligaments or bone (North et al. 2002a). Examples of nociceptive pain are burn pain and cancer pain. Also SCS is not effective for central
deafferentation pain, which is caused by CNS (central nervous system) damage from a stroke or spinal cord injury (Alfano et al. undated).

Patients are often tested psychometrically to gauge degree of emotional stability, acceptable medication usage, depression, and cooperation with rehabilitation programs, since psychological overlay is thought to explain (at least in part) many SCS failures (North et al. 2002a).

A screening trial period, of several days to several weeks, with temporary percutaneous placement of the leads and using an external generator is now an indispensable step in assessing whether the treatment is appropriate for individual patients. This phase allows for assessment of the amount of pain relief obtained with usual activities. If a patient achieves at least 50% of pain relief (Kemler et al. 2000), the temporary leads are replaced by permanent ones and additional equipment, such as the generator and the extension, is implanted (Furlan et al. 2003).
2. Methodology

A systematic search of MEDLINE (from inception until April 2003 Week 2), PREMEDLINE (from inception until 22 April 2003), and the Cochrane Library (Issue 2, 2003) using MESH (spinal cord and electric stimulation therapy) and free text (spinal cord stimulation or SCS) search terms. Searches were conducted without language restriction. In the case of duplicate publications, the latest and most complete study was included.

Table 1 provides a descriptive summary of the included studies.

Table 1. Included Studies

<table>
<thead>
<tr>
<th>Indication</th>
<th>RCTs (level II)</th>
<th>Intervention</th>
<th>N</th>
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<tbody>
<tr>
<td>1. ANGINA</td>
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<tr>
<td>b</td>
<td>De Jongste et al. 1994</td>
<td>early versus delayed implantation</td>
<td>8 early, 9 delayed</td>
</tr>
<tr>
<td>c</td>
<td>Di Pede et al. 2001</td>
<td>SCS switched on and off in the same patient</td>
<td>crossover: 15 patients</td>
</tr>
<tr>
<td>d</td>
<td>Hautvast et al. 1998</td>
<td>SCS versus implant not switched on</td>
<td>13 SCS, 12 control</td>
</tr>
<tr>
<td>2. FAILED BACK SURGERY SYNDROME</td>
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<td>e</td>
<td>North (North et al. 1994; North et al. 1995; North et al. 2002)</td>
<td>SCS versus reoperation</td>
<td>12 SCS, 15 reoperation</td>
</tr>
<tr>
<td>3. CRITICAL LIMB ISCHAEMIA</td>
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<tr>
<td>f</td>
<td>Jivegard et al. 1996</td>
<td>SCS versus analgesic treatment (control)</td>
<td>25 SCS, 26 control</td>
</tr>
<tr>
<td>g</td>
<td>Netherlands (Klomp et al. 1999; Spincemaille et al. 2000a, Spincemaille et al. 2000b; Ubbink et al. 1999)</td>
<td>SCS versus best medical treatment (BMT)</td>
<td>60 SCS, 60 BMT</td>
</tr>
<tr>
<td>4. COMPLEX REGIONAL PAIN SYNDROME (CHRONIC REFLEX SYMPATHETIC DYSTROPHY)</td>
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<td>h</td>
<td>Kemler (Kemler et al. 2001; Kemler et al. 2002; Kemler et al. 2000)</td>
<td>SCS versus physiotherapy (PT)</td>
<td>36 SCS, 18 PT</td>
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<tr>
<td>5. PAINFUL DIABETIC NEUROPATHY</td>
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<td>i</td>
<td>Tesfaye Tesfaye et al. 1996; Tesfaye et al. 1995; Tesfaye et al. 1997</td>
<td>SCS versus placebo ‘stimulation’</td>
<td>crossover: 10 patients</td>
</tr>
</tbody>
</table>
Excluded RCTs

Four RCTs were excluded from this review:

- Claeyss and Horsch 1998, SCS versus prostaglandin – outcome was ulcer healing rather than pain relief in patients with non-reconstructable peripheral vascular disease
- North et al. 2003 – compared manual testing of SCS combinations with an automated patient-interactive system
- Harke et al. 2001 – compared two analgesic drugs after all patients had received SCS
- North et al. 1999; North et al. 2002b – compared two types of electrodes for SCS (percutaneous and laminectomy)

Two Cochrane systematic reviews in preparation were identified, but no studies have yet been included in these protocols (Furlan et al. 2003; Ubbink and Vermeulen 2003). Furlan et al. 2003 will address SCS for chronic pain excluding patients with angina pectoris, cancer pain or peripheral vascular diseases; and Ubbink and Vermeulen 2003 will address SCS for non-reconstructable chronic critical leg ischaemia.

Data Extraction and Synthesis

Data were extracted by one researcher and checked by a second and checked by a second using standardised data extraction tables that were developed a priori. Included studies were examined in terms of design or execution for factors that may have introduced bias. Major efficacy and safety outcomes were not pooled, as the outcome measures reported differed between studies.
3. Results

See Appendix A

Detailed results for each study by type of intervention are presented in Appendix A.

Angina

Four RCTs of SCS for treating angina pain were located and included. One of these, the ESBY trial (Mannheimer et al. 1998, Andrell et al. 2003, Norrsell et al. 2000) compared SCS with selected patients not anticipated to benefit from CABG and one RCT compared early implantation with delayed implantation (De Jongste et al. 1994). Two RCTs compared SCS with a control – one control was a SCS device which was implanted but not switched on (Hautvast et al. 1998) and the other compared the SCS device when it was switched on and off in the same patient (Di Pede et al. 2001).

Safety

Mortality

In the ESBY trial, one out of fifty-three (1.9%) SCS patients died of myocardial infarction three months after implantation and seven out of fifty-one (13.7%) CABG patients died (six due to cardiac causes and one due to myocardial and cerebral infarctions, with three patients dying before surgery). This represents significantly less mortality in the SCS group on an intention-to-treat basis (p=0.02). After one year, three out of seventeen (17.6%) patients in the De Jongste study had died – one from paroxysmal atrial fibrillation and two deaths unrelated to SCS (one due to gradually deteriorating heart failure and one during a unrelated surgical procedure).

Morbidity

In the ESBY trial, no differences were seen between the SCS and the CABG groups for cardiac events at six months but there were significantly less cerebrovascular events in the SCS group with 2/53 (3.8%) events compared to 8/51 (15.7%) in the CABG group, p=0.03. Total cardiac and cardiovascular morbidity approached, but did not quite reach, statistical significance in favour of SCS with 8/53 (15.1%) compared to 14/51 (27.5%) in the CABG group, p=0.08.
Complications
No complications were recorded in either group in Hautvast et al. 1998 up to six weeks after implantation. Similarly De Jongste et al. 1994 did not see any peri-operative complications in either group, but two out of seventeen (11.8%) patients had electrode dislodgements which required intervention in the follow-up period. The ESBY trial reported that there were no serious complications seen with SCS. Di Pede et al. 2001 did not report any safety data.

Efficacy
Hautvast et al. 1998 was the only study to report pain. At six weeks, they found a statistically significant difference in favour of SCS when it was turned on, compared to when it was turned off (p=0.03). Number of angina attacks was significantly reduced (to one or two episodes a day) with SCS on, compared with a group yet to be implanted (De Jongste et al. 1994) or with the device turned off (Hautvast et al. 1998). This difference was not seen in Di Pede et al. 2001 for patients when they were in the ‘on SCS’ compared to the ‘off SCS’ period, but this may have been due to carry-over effects from the ‘on’ period. No difference in number of angina attacks was seen when SCS was compared to CABG (ESBY trial) although both the SCS and CABG groups showed significantly fewer attacks at six months (less than one a day) compared to baseline. Number of ischaemic episodes was significantly reduced with SCS on, compared with the device turned off (Hautvast et al. 1998) and for patients in the ‘on SCS’ period compared to the ‘off SCS’ period (Di Pede et al. 2001). However in the ESBY trial, there were significantly fewer ischaemic episodes at six months in the CABG group than the SCS group, p<0.05. SCS patients consumed significantly fewer nitrate tablets than the group yet to be implanted in the De Jongste study, but no differences in nitrate tablet consumption were seen in either the Hautvast (SCS versus inactive device), Di Pede (SCS on or off), or the ESBY (SCS versus CABG) trials.

Failed back surgery syndrome
One RCT (North et al. 1994; North et al. 1995; North et al. 2002) was located and included. The initial phase of this RCT was a parallel trial of SCS versus reoperation. After 6 months, the participants were then given a choice of crossover to the other treatment (i.e. failed SCS to reoperation; failed reoperation to SCS).

Safety
No safety data were reported in any of the North et al. papers.
**Efficacy**

At six months, 2/12 (17%) SCS patients opted for reoperation and 10/15 (67%) reoperated patients opted for SCS, \( p=0.018 \). North states that SCS was significantly better than reoperation for 90% of patients at three year follow-up, but detailed findings were not presented.

**Critical limb ischaemia**

Two RCTS were located and included. Jivegard *et al.* 1996 compared SCS (25 patients) and analgesic treatment only (26 patients) and the Netherlands multi-centre trial (Klomp *et al.* 1999; Spincemaille *et al.* 2000a, Spincemaille *et al.* 2000b; Ubbink *et al.* 1999) compared SCS with best medical treatment (BMT), with 60 patients in each arm.

**Safety**

No differences in disease-related mortality at two years were detected in the Netherlands trial (5% for SCS, 9% for BMT, \( p=0.45 \)). A total of 25 complications were reported for the SCS group and 10 BMT patients reported 12 complications. SCS complications included 13 lead displacements in two years, six implant failures, three battery failures and three infections in the subcutaneous pocket of the pulse generator. These required fourteen lead replacements, three reimplantations and one temporary and nine definitive removal of the pulse generator. Four SCS patients also reported other complications including one duodenal perforation, two cases of nausea and one case of pruritus. There were no lead fractures, epidural infections, haematomas or cerebrospinal fluid leakage. The 12 BMT complications consisted of three upper GI bleeding, seven cases of nausea and two cases of dizziness.

Jivegard *et al.* 1996 did not report any safety outcomes in the abstract.

**Efficacy**

No difference in overall survival or survival at two years without major amputation was seen in the Netherlands trial, and neither of the two studies showed differences in limb survival between groups.

Jivegard *et al.* 1996 noted that long-term pain relief was only observed in the SCS group, not the analgesia group, while the Netherlands trial did not show differences in pain between the SCS and BMT groups. In the Netherlands trial, SCS patients took less pain medication than the BMT patients at one, three and six months, but
no differences between the groups were seen at zero, twelve and eighteen months. No differences in quality of life were seen between the SCS or BMT groups in the Netherlands trial.

**Complex regional pain syndrome (chronic reflex sympathetic dystrophy)**

One RCT (Kemler et al. 2001; Kemler et al. 2002; Kemler et al. 2000) was located and included. This study compared SCS plus physiotherapy (PT) with physiotherapy alone. Originally 36 patients were randomised to SCS+PT and 18 to PT; however 12 of the 36 (33%) SCS+PT patients failed to respond adequately to SCS and then received PT only for the rest of the study. Thus 24 patients received SCS+PT and 30 received PT only.

**Safety**

Nine out of twenty-four (38%) SCS patients had a total of 17 complications during the 12 months after implantation. Complications included dural puncture in two patients (one resulting in headache); one infection which required removal of the implant and subsequent reimplantation; painful pulse-generator pocket needing modification or plug wound needing revision in six patients; a defective lead was replaced in one patient; and there were six unsatisfactory lead positionings (required eight corrective procedures).

**Efficacy**

Pain at six months was significantly reduced in the SCS+PT group compared to the PT group, p<0.001. The SCS+PT group dropped an average of 2.4 cm [standard deviation (SD) 2.5] on visual analogue scale (VAS) from baseline, while the PT group showed a very small increase, mean 0.2 [SD 1.6]. Health related quality of life did not show any significant differences between SCS+PT and PT at six months, but SCS+PT patients showed significantly better scores than PT at 12 months, p=0.004. Functional status at six months did not differ significantly between the two groups over a range of measures (and did not show a significant change over baseline for either group). No reduction in painful sensory symptoms was seen with SCS+PT compared to PT alone. These analyses were all done on an intention-to-treat basis, but the as-treated analyses showed similar findings (with SCS+PT showing a more favourable effect than the intention-to-treat analyses).
Painful diabetic neuropathy

One RCT (Tesfaye et al. 1996) was located and included. This was a crossover study of percutaneous SCS and placebo ‘stimulation’ in 10 patients.

Safety

One patient died from unrelated causes. Two patients required reinsertion of leads, which had migrated, and two patients required antibiotics for superficial wound infections.

Efficacy

Eight of ten (80%) patients had significant pain reduction (more than 50%) with the percutaneous SCS implant and were converted to permanent SCS. One of these eight (12.5%) patients ceased to benefit at four months and one of the eight died (12.5%). The remaining six patients continued to use SCS as the sole treatment for their neuropathic pain. At 14 months median follow-up, median pain (VAS) did not quite reach statistical significance in favour of SCS compared to placebo stimulation (p=0.06), but peak pain did (p=0.03).
4. Discussion

Small numbers in the studies often meant that there was a lack of power to detect clinically important differences, but the RCTs were generally of reasonable quality. Interpretation of the results was hampered by the very different comparators used (ranging from placebo to CABG).

Surprisingly, pain was measured as an outcome in only five of the nine included studies. When measured, patients generally achieved short term pain relief with SCS compared to the alternative treatment or no treatment. Hautvast et al. 1998 was the only angina trial to measure pain, finding that SCS was more effective at relieving pain than placebo (SCS turned off) at six weeks. However, SCS was associated with fewer anginal attacks when compared to placebo (Hautvast et al. 1998) or delayed implantation (De Jongste et al. 1994) but no difference was seen when SCS was compared with CABG (ESBY) or in the on/off crossover trial of Di Pede et al. 2001. For critical limb ischaemia, Jivegard et al. 1996 found SCS to be better than analgesia in relieving pain, but the Netherlands study did not find a difference between SCS plus best medical treatment and best medical treatment alone. For patients with complex regional pain syndrome, Kemler et al. 2001, Kemler et al. 2000 and Kemler and Furnee 2002 found that SCS was more effective than physiotherapy for pain relief. However Tesfaye et al. 1996, Tesfaye et al. 1995 and Tesfaye et al. 1997 did not find a difference between SCS and placebo stimulation when median pain score was measured at 14 months in patients with painful diabetic neuropathy, indicating that pain relief from SCS may not be sustained in the long-term – or alternatively that there is a strong placebo effect, since both SCS and placebo showed significantly more pain relief compared to baseline.

For failed back surgery syndrome, North et al. reported that fewer SCS patients wished to opt for reoperation than reoperated patients wanting SCS; and in patients with painful diabetic neuropathy, reported by Tesfaye et al., six out of the original ten patients were continuing to use SCS as their sole pain relief treatment at a median of 14 months after implantation.

Most complications reported in RCTs are electrode or lead displacements, which require reoperation and repositioning. A small number of implant and battery failures have been noted, as has one duodenal perforation and two dural punctures. Infection at the implant site seems to be relatively common. These findings are broadly consistent with the data from case series, although North et al. 2002a observed that lead migration has steadily declined as the SCS technology improved, with migration rates in multichannel systems down to 7%.
Cost Considerations

SCS costs were found to be lower than CABG in one RCT (ESBY) and less costly than physiotherapy after three years in the Kemler trial. However the Netherlands trial found SCS to be more costly than best medical treatment. In a non-randomised comparison, Kumar et al. 2002 also found that SCS was initially more costly than best medical treatment/conventional pain therapy, but after 2.5 years, this position was reversed with SCS showing as less costly in the remaining half of the five year follow-up period. A study modeling SCS costs against surgery and other interventions for failed back surgery syndrome, found that SCS pays for itself within 5.5 years and within 2.1 years in the subset of patients for whom SCS works (Bell et al. 1997). In 2000, the cost of implanting each device (excluding hospital and clinical costs) was between AUS $8,000 and 10,000 (Kavar et al. 2000).

The Medtronic (Minneapolis, MN) neurostimulation systems are available in Australia and are registered with the Therapeutic Goods Administration (TGA). There about 60 to 70 surgeons implanting these devices in Australia, averaging one to two implants per week.
5. Conclusions

SCS was shown to be effective in relieving pain in only some of the included studies, but the small patient numbers may have limited the ability of studies to detect clinically important differences. SCS appears to be relatively safe, although the long-term safety and effectiveness of SCS have not yet been evaluated.
References

Included studies

ANGINA

a) ESBY


- Norrsell H, Pilhall M, Eliasson T, Mannheimer C. Effects of spinal cord stimulation and coronary artery bypass grafting on myocardial ischemia and heart rate variability: further results from the ESBY study. *Cardiology* 2000;94:12-8


FAILED BACK SURGERY SYNDROME

e) North


CRITICAL LIMB ISCHAEMIA

g) Netherlands


COMPLEX REGIONAL PAIN SYNDROME

h) Kemler


PAINFUL DIABETIC NEUROPATHY

i) Tesfaye


Other references


Appendix A

Tables of Key Efficacy and Safety Findings

Abbreviations used in tables:
ADL  Daily Activity Score
CABG  Coronary Artery Bypass Grafting
CAD  Coronary Artery Disease
CRPS  Complex Regional Pain Syndrome
ECG  Electrocardiogram
ESBY  Electrical Stimulation versus Coronary Artery Bypass Surgery
GTN  Glyceryl trinitrate intake
IASP  International Association for the Study of Pain
IQR  Interquartile Range
ITT  Intention to Treat
LVEF  Left Ventricle Ejection Fraction
RCT  Randomised Controlled Trial
MI  Myocardial Infarction
NYHA  New York Heart Association
pns  probability not significant
PT  Physical Therapy
PTCA  Percutaneous Transluminal Coronary Angioplasty
QALY  Quality-Adjusted Life Year
QOL  Quality of Life
SAS  Social Activity Score
SCS  Spinal Cord Stimulation
SD  Standard deviation
sem  Standard error of the mean
VAS  Visual Analogue Scale
### Appendix A: Key Efficacy and Safety Findings - Randomised Controlled Trials

<table>
<thead>
<tr>
<th>Study details</th>
<th>Key efficacy findings</th>
<th>Key safety findings</th>
<th>Appraisal/Comments</th>
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<tr>
<td><strong>Randomised controlled trial</strong>&lt;br&gt;<em>ESBY – angina</em>&lt;br&gt;(Mannheimer et al. 1998; Andrell et al. 2003; Norrsett et al. 2000)&lt;br&gt;January 1992 to March 1995.&lt;br&gt;104 participants – 53 SCS, 51 CABG&lt;br&gt;Epidural space punctured at T6, quadripolar electrode tip placed at T1 to T2.&lt;br&gt;Two stimulation strengths, one strong for anginal pain and one weaker to be used prophylactically (latter used for at least 2 hours 4 times daily).&lt;br&gt;Inclusion criteria:&lt;br&gt;Patients with no proven prognostic benefit from CABG and an increased risk of complications.&lt;br&gt;Exclusion criteria:&lt;br&gt;Unsuitable for CABG, unable to manage the SCS device, unable to follow the study protocol, MI within last 6 months.</td>
<td>Self assessed response to treatment&lt;br&gt;SCS 83.7%; CABG 79.5%&lt;br&gt;<em>Number of anginal attacks per day at 6 months&lt;br&gt;SCS 0.7 [1.3] (n=49); CABG 0.5 [1.3] (n=36), pns significant reduction from baseline (p&lt;0.0001) seen for both groups.&lt;br&gt;Overall mortality&lt;br&gt;8 (between randomization and 6 month follow-up)&lt;br&gt;- 1 (1.9%) SCS (MI 3 months after implantation)&lt;br&gt;7 (13.7%) CABG (3 before surgery), 6 cardiac, 1 myocardial and cerebral infarctions&lt;br&gt;Cardiac events (6 months)</em>&lt;br&gt;No difference seen between the two groups.&lt;br&gt;Cerebrovascular events (6 months)*&lt;br&gt;2 (3.8%) SCS; 8 (15.7%) CABG, p=0.03&lt;br&gt;Total cardiac and cerebrovascular morbidity**&lt;br&gt;8 (15.1%) SCS; 14 (27.5%) CABG, pns (0.08)&lt;br&gt;*2 SCS patients and 3 CABG patients had both cardiac and cerebrovascular events.&lt;br&gt;**Includes patients who had one or more fatal or nonfatal cardiac or cerebrovascular event.</td>
<td>Overall mortality&lt;br&gt;8 (between randomization and 6 month follow-up)&lt;br&gt;- 1 (1.9%) SCS (MI 3 months after implantation)&lt;br&gt;7 (13.7%) CABG (3 before surgery), 6 cardiac, 1 myocardial and cerebral infarctions&lt;br&gt;Cardiac events (6 months)<em>&lt;br&gt;No difference seen between the two groups.&lt;br&gt;Cerebrovascular events (6 months)</em>&lt;br&gt;2 (3.8%) SCS; 8 (15.7%) CABG, p=0.03&lt;br&gt;Total cardiac and cerebrovascular morbidity**&lt;br&gt;8 (15.1%) SCS; 14 (27.5%) CABG, pns (0.08)&lt;br&gt;*2 SCS patients and 3 CABG patients had both cardiac and cerebrovascular events.&lt;br&gt;**Includes patients who had one or more fatal or nonfatal cardiac or cerebrovascular event.</td>
<td>Potential for bias:&lt;br&gt;- randomized, but no details given of method of allocation concealment&lt;br&gt;- open study, patients and outcome assessors unable to be blinded&lt;br&gt;- reports analysis on an an intention-to-treat basis, but this has not been done for all outcomes&lt;br&gt;Loses to follow-up:&lt;br&gt;6 months&lt;br&gt;16 – 12 CABG (7 died, 2 not operated on – 1 too risky, 1 anginal symptoms resolved before surgery, 3 lack of compliance or medical complications not related to the study); 4 SCS (2 emergency CABG due to unstable angina, 1 died, 1 lack of compliance or medical complications not related to study. 2 years&lt;br&gt;2 CABG patients declined participation in the follow-up, leaving 49 patients in the CABG group and 53 in the SCS group.&lt;br&gt;Crossover:&lt;br&gt;3 patients randomized to CABG received SCS instead (1 refused CABG, 1 too high risk and 1 was implanted with SCS 2 months after CABG due to severe angina). 3 patients randomised to SCS had CABG because of unstable angina.&lt;br&gt;Other:&lt;br&gt;-complete statistics not always reported e.g. only percentages given for some outcomes&lt;br&gt;-denominators not always clear</td>
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<tr>
<td>Study details</td>
<td>Key efficacy findings</td>
<td>Key safety findings</td>
<td>Appraisal/Comments</td>
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<tr>
<td><strong>Randomised controlled trial</strong></td>
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<tr>
<td><strong>De Jongste et al. 1994 – angina</strong></td>
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<td>17 participants – 8 implanted with SCS within 2 weeks of being referred from cardiologist; 9 implanted after 8 weeks.</td>
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<td>After the randomized 8 week period, the control group received SCS devices under similar protocols to the SCS 2 week group.</td>
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<tr>
<td>Stimulation applied three times a day for 1 hour plus elective use during angina attacks. Either a unipolar or quadripolar electrode was inserted between T4 and T5 of the epidural space, with final position usually T1.</td>
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<tr>
<td>Follow-up: 1 year.</td>
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<td><strong>Inclusion criteria:</strong></td>
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<td>Intractable angina, with angiographically documented significant CAD (maximum 6 months before inclusion), not suitable for revascularization procedures such as CABG or PTCA, NYHA functional class III or IV angina pectoris, reversible ischaemia documented at least by a symptom-limited treadmill exercise test, pharmacologically optimal drug treatment for at least 1 month.</td>
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<tr>
<td><strong>Exclusion criteria:</strong></td>
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<tr>
<td>Inability to perform treadmill exercise tests, age &gt;76 years, MI or unstable angina during the last 3 months, somatic spine disorders, leading to insurmountable technical problems, significant valve abnormalities demonstrated by ECG.</td>
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<tr>
<td><strong>Exercise duration, mean (sec) at 6 to 8 weeks</strong></td>
<td></td>
<td>Perioperative complications</td>
<td></td>
</tr>
<tr>
<td>SCS 827 [sem138]; control 694 [sem67], p&lt;0.05</td>
<td>None in either group.</td>
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<tr>
<td><strong>Time to angina (sec) at 6 to 8 weeks</strong></td>
<td></td>
<td>Complications during randomization period</td>
<td></td>
</tr>
<tr>
<td>SCS 691 [sem174]; 438 [sem91]</td>
<td>None in either group.</td>
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<tr>
<td><strong>Angina pectoris episodes (per week) at 6 to 8 weeks</strong></td>
<td></td>
<td>Complications during follow-up</td>
<td></td>
</tr>
<tr>
<td>SCS 9.0 (4 to 14.2); control 13.6 (7.7 to 20.8), p&lt;0.05</td>
<td>2 patients had electrode dislodgements requiring intervention.</td>
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<tr>
<td><strong>GTN, median (per week) at 6 to 8 weeks</strong></td>
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<tr>
<td>SCS 1.6 (0.3 to 6.9); control 8.5 (2.8 to 27.1), p&lt;0.05</td>
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<tr>
<td><strong>ADL score, median, at 6 to 8 weeks</strong></td>
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<tr>
<td>SCS 2.06 (95% CI 1.65 to 2.26); control 1.25 (95% CI 1.1 to 1.71), p&lt;0.05</td>
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<tr>
<td><strong>S-AIS score, median, at 6 to 8 weeks</strong></td>
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<tr>
<td>SCS 2.10 (95% CI 1.61 to 2.44); 1.39 (95% CI 1.1 to 1.65)</td>
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<tr>
<td>During long-term follow-up of 1 year, both exercise and quality of life variables remained improved compared to those at baseline.</td>
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<td><strong>Potential for bias:</strong></td>
<td></td>
<td>- randomized, adequate method of allocation concealment (independent telephone service)</td>
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<td>- patients not blinded</td>
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<tr>
<td><strong>Losses to follow-up:</strong></td>
<td></td>
<td>3 patients not included in long-term follow-up – paroxysmal atrial fibrillation (1 patient) and 2 deaths unrelated to SCS (one due to gradually deteriorating heart failure and 1 during a nonrelated surgical procedure).</td>
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<tr>
<td><strong>Other:</strong></td>
<td></td>
<td>Measure of variance sometimes not specified (e.g. angina episodes).</td>
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</table>
**Study details**  | **Key efficacy findings** | **Key safety findings** | **Appraisal/Comments**
--- | --- | --- | ---
**Randomised controlled trial**

**Di Pede et al. 2001 – angina**

- **Number of ischaemic episodes**
  - On period median 3 (range 0 to 24); mean 5.2 [SD6.3]
  - Off period median 6 (range 0 to 29); mean 7.7 [SD8.4]
  - p<0.05

- **Duration of ischaemic episodes (mins)**
  - On period median 16 (range 0 to 123); mean 26.9 [SD35.2]
  - Off period median 29 (range 0 to 186); mean 48.9 [SD57.3]
  - p<0.05

- **Total ischaemic burden, (mV*min)**
  - On period median 0.8 (range 0 to 13); mean 2.7 [SD4.1]
  - Off period median 2.5 (range 0 to 19.5); mean 5.6 [SD6.8]
  - pns

- **Anginal attacks (and nitroglycerin usage), median and range**
  - On period 0.13 (0 to 1); Off period 0.13 (0 to 2)

- **Proportion of symptomatic to total ischaemic episodes**
  - On period 1.7%; Off period 2.5%

- **Inclusion criteria:**
  - Severe refractory angina pectoris (Canadian class III-IV), despite optimal drug therapy, and unsuitable for myocardial revascularisation.

- **Losses to follow-up:**
  - None during study, where only short-term outcomes were measured.

- **Other:**
  - Lack of a wash-out period may have had some carry-over effect in the ‘off’ period.

- **Potential for bias:**
  - Sequence of (single) crossover was randomized
  - Cardiologist assessing the ECGs was unaware if the period was ‘on’ or ‘off’
### Study details

### Key efficacy findings

#### Time to angina on treadmill at 6 weeks, mean (secs)
- SCS 319 [85]; Control 246 [97], p=0.01

#### Total exercise duration at 6 weeks, mean (secs)
- SCS 533 [184]; Control 427 [177], p=0.03

#### Anginal attacks per day at 6 weeks
- SCS 2.3 [1.9]; Control 3.2 [1.5], p=0.01

#### Consumption of nitrate tablets at 6 weeks
- SCS 1.6 [2.2]; Control 2.6 [1.7], pns

#### Pain at 6 weeks, VAS (cm)
- SCS 2.6 [1.4]; Control 3.2 [1.4], p=0.03

#### Quality of life at 6 weeks, LASA (cm)
- SCS 6.8 [1.0]; Control 6.2 [1.1], pns

#### Number of ischaemic episodes at 6 weeks, ECG, median and range
- SCS 0 (0-12); Control 1.0 (0-14), p=0.04

#### Total duration of ischaemia at 6 weeks, ECG, median and range (mins)
- SCS 0.0 (0-55.9); Control 1.9 (0-127.1)

### Key safety findings

#### Complications (up to 6 weeks)
- No complications recorded in either group.

### Appraisal/Comments

#### Potential for bias:
- randomized, but no details given of method of allocation concealment
- patients blinded
- no losses to follow-up
### Study details

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<tr>
<td><strong>North et al. 1994; North et al. 1995; North et al. 2002 – failed back surgery syndrome</strong></td>
<td>Opting for crossover at 6 months</td>
<td>In addition, 2 SCS patients have not elected to proceed with permanent SCS and have retained their temporary SCS device, but neither have they agreed to reoperation.</td>
<td>Potential for bias: - randomized but no details of method of allocation concealment given - outcome assessor “disinterested” but blinding not possible Other: This is a report of an interim analysis – study aimed to recruit 50 patients but no reports of the study after 1995 could be located (except for a brief mention in North et al. 2002).</td>
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</table>

27 participants – 12 SCS, 15 reoperation.

RCT with parallel (SCS vs reoperation) with choice of crossover at 6 months (failed temporary SCS to reoperation; failed reoperation to SCS) arms.

Patients randomized to SCS were implanted with a temporary percutaneous electrode for a 2 to 2.5 day trial – if patient reported at least 50% estimated pain relief, permanent implant was offered.

**Inclusion criteria:** Persistent radicular pain, with and without low back pain, following lumbosacral spine surgery.

**Exclusion criteria:** Major or disabling neurologic deficit, radiographically critical neural compression, radiographic evidence of gross instability necessitating fusion, significant untreated dependency on prescription narcotic analgesics or benzodiazepines, major psychiatric comorbidity, any other significant chronic pain problem, chief complaint of axial (low back) pain, exceeding radicular pain – hip, buttock and leg pain.
## Study details

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<td><strong>Randomised controlled trial</strong>&lt;br&gt;Netherlands (Klopp et al. 1999; Spincemaille et al. 2000a; Spincemaille et al. 2000b; Ubbink et al. 1999 – critical limb ischaemia)&lt;br&gt;Netherlands (17 hospitals): November 1991 to January 1996.&lt;br&gt;120 participants – 60 SCS plus best medical treatment; 60 best medical treatment (BMT).&lt;br&gt;SCS – lead placed in the epidural space and manipulated until appropriate paraesthesiae that extended into the painful area of the limb, were achieved.&lt;br&gt;Medical treatment included analgesics, antithrombotic drugs such as aspirin or coumarins, vasoactive drugs such as pentoxifylline, bufomedil, or ketanserin, local wound care, and antibiotics as needed.&lt;br&gt;Follow-up: 2 years – median 605 days (244 to 1171).&lt;br&gt;Inclusion criteria:&lt;br&gt;Patients with critical limb ischaemia not suitable for vascular reconstruction or reintervention, usually because of insufficient distal runoff or recurrent graft failure, persistent pain at rest for more than 2 weeks or ischaemic skin lesions, ankle systolic pressure below 50 mmHg, or in patients with diabetes and incompressible vessels, absent palpable ankle pulses.&lt;br&gt;Exclusion criteria:&lt;br&gt;Patients with vascular disorders other than atherosclerotic disease, no rest pain (e.g. only intermittent claudication), neoplastic or&lt;br&gt;Survival&lt;br&gt;SCS vs BMT hazard ratio 1.09 95% CI 0.59 to 2.03&lt;br&gt;Survival at 2 years without major amputation&lt;br&gt;SCS vs BMT hazard ratio 0.96 95% CI 0.61 to 1.51&lt;br&gt;Survival at 2 years&lt;br&gt;SCS 52%; BMT 46%, p=0.47&lt;br&gt;SCS vs BMT hazard ratio 0.81 95% CI 0.47 to 1.42&lt;br&gt;Amputation frequency by category of microcirculation at 18 months&lt;br&gt;SCS 25/60 (48%); BMT 29/60 (54%), p=0.47&lt;br&gt;SCS vs BMT hazard ratio 0.81 95% CI 0.47 to 1.42&lt;br&gt;Major amputation up to 2 years&lt;br&gt;SCS 52%; BMT 46%, p=0.47&lt;br&gt;SCS vs BMT hazard ratio 0.81 95% CI 0.47 to 1.42&lt;br&gt;Major amputation or death up to 2 years&lt;br&gt;SCS 38/60 (67%); BMT 39/60 (66%), p=0.86&lt;br&gt;Pain&lt;br&gt;mean VAS, with highest score representing maximal pain decreased significantly from baseline at 1 and 3 months for both groups (p&lt;0.001), but no difference was seen between groups – SCS 22.5; BMT 22.5 at 18 months&lt;br&gt;PRI (McGill part 1) and NHP pain score decreased significantly from baseline at 1 and 3 months for both groups, but no difference was seen between groups. However there was a significant difference between amputees and non-amputees.&lt;br&gt;Pain medication&lt;br&gt;SCS: fewer non-narcotic and narcotic drugs at 1, 3 and 6 months than BMT (p&lt;0.001, 0.001, 0.002 respectively), but no differences &lt;br&gt;Disease-specific mortality at 2 years&lt;br&gt;SCS 5%; BMT 9%, p=0.45&lt;br&gt;Complications (SCS)&lt;br&gt;- Implant failure 6&lt;br&gt;- Lead problems within 30 days - 3 patients required lead positioning&lt;br&gt;2 year follow-up - 13 lead displacements occurred&lt;br&gt;- Infection 3 patients (in subcutaneous pocket of the pulse generator)&lt;br&gt;- Battery failure 3 failed&lt;br&gt;Correction measures:&lt;br&gt;14 lead replacements&lt;br&gt;3 reimplantations&lt;br&gt;1 temporary and 9 definitive removal of the pulse generator.&lt;br&gt;Other complications – 4 patients (1 duodenal perforation, 2 nausea, 1 pruritus.&lt;br&gt;There were no lead fractures, epidural infections, haematoma or cerebrospinal fluid leakage .&lt;br&gt;Complications (BMT)&lt;br&gt;10 patients – 3 upper GI bleeding, 7 nausea, 2 dizziness</td>
<td>Potential for bias:&lt;br&gt;- Randomisation was generated by random numbers table and there was adequate allocation concealment (list held independently of the investigators and accessed by phone)&lt;br&gt;- method of blinding (if any) not reported&lt;br&gt;- analysis stated to be by intention-to-treat and per-protocol; missing values as the result of death or amputation were treated with the ‘last-observation-carried-forward’ approach&lt;br&gt;Lapses to follow-up:&lt;br&gt;SCS – 3 (1 withdrew consent, 2 leads not placed correctly), but 60 patients analysed in each group.&lt;br&gt;Other:&lt;br&gt;Study had 80% power to detect an increase in limb survival by 3 months (hazard ratio 1.8) with alpha of 5%.&lt;br&gt;some figures reported as percentages only without actual numbers.</td>
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concomitant disease restricting life expectancy to less than 1 year, ulceration deeper than the fascia or with a largest diameter of >3cm, extensive necrosis or infected gangrene, not possible to implant an epidural electrode and stimulator, and those who were terminally ill, dependent on a pacemaker, or unable to complete the questionnaire and follow-up.

Chemical lumbar sympathectomy and prostanoids were not excluded, but were used in only 3 patients.

between the groups were seen at 0 months, 12 and 18 months.

Ulcer healed at 1 year (cumulative %)
- SCS 45%; BMT 54%, p=0.21

Gangrene % at 1 year
- SCS 53%; BMT 50%, p=0.56

Quality of life
NHP and Euroqol showed poor quality of life compared with the general population, but no differences were seen between the SCS and the BMT groups. However patients undergoing SCS who were not amputated had better mobility and energy scores on NHP than the BMT non-amputated patients, p<0.01.

Costs
Total cost at 2 years was 80,439 guilders per patient for SCS, 17,376 guilders (28%) higher than BMT, p=0.009.
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<tr>
<td><strong>Randomised controlled trial</strong></td>
<td><strong>Jivegard et al. 1996 – critical limb ischaemia</strong></td>
<td><strong>Pain</strong></td>
<td><strong>Limb salvage rates at 18 months</strong></td>
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<tr>
<td></td>
<td>51 participants – 25 SCS; 26 analgesic treatment (control).</td>
<td>Long-term pain relief was only observed in the SCS group.</td>
<td>SCS 62%; analgesia only 45%, pns</td>
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<td>Follow-up: 18 months.</td>
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<td>Tissue loss</td>
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<td><strong>Inclusion criteria:</strong></td>
<td>Less in the SCS group, p&lt;0.05</td>
<td>A subgroup analysis of patients without arterial hypertension showed a significantly lower amputation rate in the SCS versus the analgesia only group.</td>
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<td>41 atherosclerotic and 10 diabetic patients having chronic leg ischaemia with rest pain and/or ischaemic ulcerations due to technically inoperable arterial occlusions.</td>
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### Study details

**Randomised controlled trial**


54 participants – 36 SCS plus physiotherapy (PT); 18 PT.

24/36 SCC+PT patients responded successfully to 1 week of test stimulation, and then received a SCS implant. The remaining 12 patients continued to participate with PT. Thus 24 patients received SCS+PT and 30 received PT.

SCS: Electrode was positioned to the posterior epidural space (generally C4 if the hand was affected and T12 if the foot was affected).

PT: standardised program of graded exercises designed to improve the strength, mobility and function of the affected hand or foot.

Follow-up: 12 months.

### Key efficacy findings

- **Pain at 6 months**
  - VAS change (cm) – ITT
    - SCS+PT -2.4 [2.5]; PT 0.2[1.6], p<0.001
  - Improvement in global perceived effect – ITT
    - SCS+PT 14/36 (39%); PT 1/18 (6%), p=0.01

- **Health related quality of life at 6 months (%) – ITT**
  - SCS+PT 6 [22]; PT 3 [18], p=0.58

- **Change in score at 12 months**
  - SCS+PT 0.22 [0.33]; PT 0.03 [0.13], p=0.004

- **Functional status at 6 months - ITT**
  - Did not differ significantly between the two groups over a range of measures (and did not show a significant change over baseline for either group).

### Key safety findings

- **Dural puncture**
  - SCS: 2 patients (with headache in one)

- **Other complications**
  - SCS – 9/24 (38%) patients had a total of 17 complications during the 12 months after implantation
    - 1 infection which required antibiotics and removal of the implant and subsequent reimplantation
    - in 6 patients a painful pulse-generator pocket was modified or plug wound needed revision (seven procedures required)
    - in 1 a defective lead was replaced
    - 6 unsatisfactory lead positionings (8 procedures required)

### Appraisal/Comments

- **Potential for bias:**
  - randomization generated by a table of random numbers and assignments were made by a research assistant and were concealed from the study investigators
  - not possible to blind any of the parties
  - results were analysed on both on both a treatment received and intention-to-treat basis

- **Losses to follow-up:**
  - 1 patient assigned to PT refused to participate; 4 patients in the PT group and 1 patient in the SCS+PT were lost to follow-up after the 6 month assessment (their 6 month assessment scores were carried forward to 12 months).

- **Other:**
  - Since the SCS+PT group showed improvement in pain and QOL after randomization but before treatment had commenced, change scores were calculated from a baseline from this period instead of prior to randomization (to lessen the impact of a possible placebo effect).
  - Some discrepancies in figures and results between the three papers reporting this study.
Exclusion criteria:
Previous diagnosis of Raynaud’s disease, history of neurologic abnormalities not related to CRPS 1; conditions affecting function of the diseased or contralateral extremity other than CRPS 1 itself; blood clotting disturbances or anticoagulant drug therapy; or an implanted pacemaker; substantial psychopathology.
**Study details** | **Key efficacy findings** | **Key safety findings** | **Appraisal/Comments**
---|---|---|---
**Randomised controlled trial**


- 10 participants – crossover between SCS or placebo 'stimulation'.
- Electrode implanted in the thoracic/lumbar epidural space and connected, in random order, to a percutaneous electrical stimulator or to a placebo stimulator; converted to permanent SCS if significant pain relief achieved.
- Permanent device consisted of 4 electrodes with lead to L1-L2, and finally positioned between T9 and T11 usually.
- Follow-up: 14 months median (IQR 9 to 19).

**Inclusion criteria:**
Patients with chronic sensory-motor diabetic neuropathy who did not respond to conventional treatment.

**Exclusion criteria:**
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 year's duration, neuropathic pain in upper limbs, and presence of peripheral neuropathies from causes other than diabetes.

- **Pain**
  8/10 had significant (VAS reductions >50%) pain relief with SCS, p<0.02 and were converted to permanent SCS. 1/8 ceased to benefit at 4 months (and 1/8 died of unrelated causes).
  - At the end of the study, 6 patients continued to gain significant pain relief and used SCS as the sole treatment for their neuropathic pain.
  - **Background pain, VAS, (median, IQR) at 14 months (n=7)**
    - SCS 23 (11 to 33); placebo 77 (72 to 84), p=0.06
    - [Both SCS and placebo showed significant improvement in pain scores over baseline.]
  - **Peak pain, VAS, (median, IQR) at 14 months (n=7)**
    - SCS 20 (14 to 54); placebo 81 (79 to 83), p=0.03
  - **McGill pain questionnaire**
    - SCS significant improvement in the four components at the end of the study compared to baseline; no difference over baseline seen with placebo.

- **Mortality**
  - 1 patient died of unrelated causes.

- **Lead migration**
  - 2 patients, required reinsertion.

- **Superficial wound infection**
  - 2 patients required antibiotics.

- **Potential for bias:**
  - Randomised, but method of allocation concealment not stated.
  - Patients were initially blinded, but authors report that the blinding was ‘broken’ as patients became used to the SCS sensations.

- **Losses to follow-up:**
  - 1 death, but results up until time of death (2 months after SCS implantation) were included.