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[Intervention Review]

Spinal cord stimulation for non-reconstructable chronic critical leg ischaemia

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ABSTRACT

Background

Patients suffering from inoperable chronic critical leg ischaemia (NR-CCLI) face amputation of the leg. Spinal cord stimulation (SCS) has been proposed as a helpful treatment in addition to standard conservative treatment.

Objectives

To find evidence for an improvement on limb salvage, pain relief, and the clinical situation using SCS compared to conservative treatment alone.

Search methods

For this update the Cochrane Peripheral Vascular Diseases Group Trials Search Co-ordinator searched the Specialised Register (last searched January 2013) and CENTRAL (2012, Issue 12).

Selection criteria

Controlled studies comparing the addition of SCS with any form of conservative treatment to conservative treatment alone in patients with NR-CCLI.

Data collection and analysis

Both authors independently assessed the quality of the studies and extracted data.

Main results

Six studies comprising nearly 450 patients were included. In general the quality of the studies was good. No study was blinded due to the type of intervention.

Limb salvage after 12 months was significantly higher in the SCS group (risk ratio (RR) 0.71, 95% confidence interval (CI) 0.56 to 0.90; risk difference (RD) -0.11, 95% CI -0.20 to -0.02). Significant pain relief occurred in both treatment groups, but was more prominent in the SCS group where the patients required significantly less analgesics. In the SCS group, significantly more patients reached Fontaine stage II than in the conservative group (RR 4.9, 95% CI 2.0 to 11.9; RD 0.33, 95% CI 0.19 to 0.47). Overall, no significantly different effect on ulcer healing was observed with the two treatments.

Complications of SCS treatment consisted of implantation problems (9%, 95% CI 4 to 15%) and changes in stimulation requiring re-intervention (15%, 95% CI 10 to 20%). Infections of the lead or pulse generator pocket occurred less frequently (3%, 95% CI 0 to 6%). Overall risk of complications with additional SCS treatment was 17% (95% CI 12 to 22%), indicating a number needed to harm of 6 (95% CI 5 to 8).

Average overall costs (one study) at two years were EUR 36,500 (SCS group) and EUR 28,600 (conservative group). The difference (EUR 7900) was significant ($P < 0.009$).

Authors' conclusions

There is evidence to favour SCS over standard conservative treatment alone to improve limb salvage and clinical situations in patients with NR-CCLI. The benefits of SCS must be considered against the possible harm of relatively mild complications and the costs.

PLAIN LANGUAGE SUMMARY

Spinal cord stimulation for patients with chronic critical leg ischaemia who cannot have blood vessel surgery

Peripheral arterial disease is relatively common, particularly in late middle age. Blockages in the leg arteries can reduce blood flow in the legs enough to cause fatigue and pain in the muscles when walking (called intermittent claudication). This can become severe and cause critical limb ischaemia which can result in rest pain, leg ulceration, and gangrene that requires amputation. Surgery may improve blood flow but is not possible for everybody. Drugs may be used to relieve pain, improve leg circulation, and treat infection. Another option for patients who cannot have surgery is spinal cord stimulation (SCS). This involves stimulating nerves in the spine to help reduce pain and increase healing of ulcers by improving the local blood circulation in the affected leg. The review authors included five randomised and one controlled clinical trial involving a total of nearly 450 patients. In general the quality of the studies was good. Amputation after 12 months was required less often when SCS was added to standard care. Significant pain relief occurred with and without SCS but patients in the SCS group required fewer pain killers. Overall there was no difference on ulcer healing rates between the two treatment groups. Complications of SCS treatment consisted of problems with initially implanting the electrodes, in 8% of patients, and the need for repeat surgery because of electrode or lead failures in 12% of patients; infections occurred less frequently (3%). The average overall costs at two years were calculated in one study and found to be EUR 36,500 in the SCS group and EUR 28,600 in the conservative treatment alone group.

BACKGROUND

The treatment of chronic critical limb ischaemia (CCLI) is a challenge in vascular medicine since comorbidity (the presence of two or more coexisting medical conditions) and mortality are high due to the presence of systemic atherosclerosis. The natural history of CCLI is difficult to describe because of differences in definitions used and the proportion of patients who are revascularised. It is estimated that 10% to 30% of patients with CCLI will die within six months and another 25% to 35% will undergo a major amputation (TASC 2000a). Revascularisation (surgical restoration of blood flow to an organ) is the therapy of choice in CCLI patients, used to relieve ischaemic rest pain, heal ischaemic ulcers or gangrene, and to avoid major (foot or higher) amputation (TASC 2000b). Nevertheless, for some patients vascular surgery has no realistic chance of success despite technical progress, an aggressive surgical approach, and repetitive reconstructions. Their pain is often disabling, adversely affects their quality of life and severely limiting their activity levels.

The only option for these patients with non-reconstructable chronic critical leg ischaemia (NR-CCLI), so far, is conservative treatment consisting of analgesics, vasodilators, and anticoagulants; before amputation ultimately becomes necessary. Alternative or additional therapies have been sought to improve limb salvage and quality of life. These include surgical interruption of the sympathetic nerves to promote vasodilation and relieve pain (sympathectomy), or spinal cord stimulation (SCS). SCS has been proposed as an aid in the management of chronic, intractable pain of the trunk or limbs. Several pre-clinical and clinical studies using SCS have been performed to investigate potential beneficial effects such as reduction in amputation rate, pain relief, and healing of ulcers. The most desired effect is limb salvage.

Cook et al were the first investigators to use SCS in patients with peripheral vascular disease (Cook 1976). They reported a striking relief of pain and increased healing of ulcers. In some publications SCS appeared to provide good-to-excellent pain control in 60% to 82% of patients (Bunt 1991; Claeys 1998; Fiume 1989; Horsch 1994; Jacobs 1990; Kumar 1997; Mingoli 1993; Rickman 1994; Tesfaye 1996). A reduction in use of oral pain medications was found (Mingoli 1993; Spiegelmann 1991; Tesfaye 1996) whilst others described an improvement in claudication distance (Tallis 1983). Increases in skin temperature have been registered by thermographic recordings and measurements of skin temperature (Augustinsson 1985; Broseta 1986). Improvements in activities of daily living were also shown (Fiume 1989; Linderth 1992; Rickman 1994; Spiegelmann 1991; Tesfaye 1996). These results have been confirmed by other studies (Augustinsson 1985; Broseta 1986; Jacobs 1990).

Postulated beneficial effects of SCS on the ischaemic leg could be attributed to an improvement in the microcirculatory status of the limb. The nutrition of the skin is determined by the peripheral microcirculatory blood flow. Several authors saw an increase in direct and indirect parameters of skin microcirculation, such as capillary flow and density of capillaries perfused (Jacobs 1990), as well as skin temperature of the foot (Augustinsson 1985; Broseta 1986). Local transcutaneous oxygen tension (T_{cpO₂}) was suggested as a predictive factor of success (Galley 1994; Gersbach 1997; Kumar 1997; Spincemille 2001; Ubbink 1999). Doppler ultrasound recordings showed a tendency toward normalisation of the pulse

wave morphology (Broseta 1986). However, few of the above-mentioned studies were randomised or controlled.

OBJECTIVES

To identify and summarise the evidence for the effectiveness of SCS in the treatment of patients suffering from non-reconstructable chronic critical leg ischaemia (NR-CCLI) as compared with conservative treatment alone. This usually consists of analgesic, vasodilatory or anticoagulant medications and local wound care.

Primary objective

To assess the effect of SCS on limb salvage.

Secondary objective

To assess the effect of SCS on pain relief, wound healing, quality of life, costs and complications caused by SCS.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) evaluating the effectiveness of SCS in patients with NR-CCLI. Controlled clinical trials (CCTs) were also included as it was expected that the number of RCTs would be limited.

To be in agreement with the reporting standards definition of CCLI (TASC 2000c), these studies had to present an objective measure of peripheral arterial disease, such as a systolic ankle blood pressure < 50 mm Hg, a toe blood pressure < 30 mm Hg, a T_{cpO₂} < 30 mm Hg, to ensure that the clinical manifestations of CCLI were indeed caused by peripheral arterial disease.

Studies with patients suffering from severe peripheral arterial disease according to their peripheral pressures but without symptoms of CCLI (subcritical ischaemia) were excluded.

Types of participants

Inclusion criteria

Men and women aged over 18 years with atherosclerotic non-reconstructable chronic critical leg ischaemia (NR-CCLI).

Chronic critical leg ischaemia was defined according to the TransAtlantic Inter-Society Consensus document (TASC 2000c), which is based on the clinical symptoms predominantly caused by peripheral arterial disease (that is ischaemic rest pain and ulceration).

Non-reconstructability was defined as the situation in which the treating physician saw no surgical options for the patient to treat the critically ischaemic leg at the time of trial inclusion. This can occur when no crural arteries can be found on the angiogram, as potential sites for a distal bypass procedure; no suitable veins are available as bypass material; or when the patient's condition precludes an operation.

Exclusion criteria

The term 'atherosclerotic' excluded patients suffering from critical leg ischaemia solely due to non-atherosclerotic vascular diseases,

like Raynaud's disease or Buerger's disease. Inclusion of these patients would cause an undesired heterogeneity of the study population.

Milder forms of leg ischaemia, in particular intermittent claudication, are not considered suitable for SCS treatment because this condition does not generally require vascular reconstruction.

Types of interventions

SCS treatment was compared with other forms of non-surgical treatment, such as analgesics, vasodilatory or anticoagulant medications (including prostaglandins) and local wound care.

Types of outcome measures

Primary outcomes

Limb salvage, which ended the moment a major (foot or higher) amputation took place.

Secondary outcomes

Pain relief, wound healing, SCS complications, quality of life, and costs; according to the scales used in the various articles.

Search methods for identification of studies

Searches were not limited by language or publication status.

Electronic searches

For this update the Cochrane Peripheral Vascular Diseases Group Trials Search Co-ordinator (TSC) searched the Specialised Register (last searched January 2013) and the Cochrane Central Register of Controlled Trials (CENTRAL) 2012, Issue 12, part of *The Cochrane Library*, (www.thecochranelibrary.com). See (Appendix 1) for details of the search strategy used to search CENTRAL. The Specialised Register is maintained by the TSC and is constructed from weekly electronic searches of MEDLINE, EMBASE, CINAHL, AMED, and through handsearching relevant journals. The full list of the databases, journals and conference proceedings which have been searched, as well as the search strategies used are described in the (Specialised Register) section of the Cochrane Peripheral Vascular Diseases Group module in *The Cochrane Library* (www.thecochranelibrary.com).

For the original review, the authors searched MEDLINE, EMBASE, and CINAHL using a search strategy devised from the key words listed in (Appendix 2).

Searching other resources

We contacted authors of included RCTs or CCTs for additional data or unpublished studies, and searched the bibliographies of the trials identified through the search process. We also approached the research centre of the major manufacturer of neurostimulators (Bakken Research Centre, Maastricht, The Netherlands). They were not aware of any recently finished or ongoing studies at the time of updating the review.

Data collection and analysis

Selection of studies

The titles and abstracts of references identified by the search were screened independently by two authors (DU, HV) for their potential

relevance and design. Full versions of articles were obtained and checked independently to identify those that met the inclusion criteria.

Assessment of methodological quality

The methodological quality of each trial was systematically assessed by the same two authors (DU, HV). A third independent referee (ASG) from the Department of Clinical Epidemiology and Biostatistic assessed the two trials co-authored by DU. The assessment was performed according to the Dutch Cochrane Centre list of factors (Dutch CC) relating to internal and external validity. This list includes the following.

1. Was allocation of intervention randomised?
2. Was allocation concealed from the researcher who included the patients?
3. Was the proportion of participants with completed follow up > 80%?
4. Was an intention-to-treat analysis used?
5. Were all participants blinded to the intervention?
6. Were all healthcare workers blinded for the intervention?
7. Were all outcome assessors blinded for the intervention?
8. Were both groups comparable at baseline?
9. Were both groups, apart from the investigated intervention, treated the same?
10. Are the results of this trial valid and applicable?
11. Was the sample size based on a proper a priori calculation?

Data collection and extraction

Details of the studies selected were extracted and summarised independently by two authors (DU, HV) using a data extraction sheet from the Dutch Cochrane Centre (Dutch CC). If data were missing from reports of trials, attempts were made to contact the authors to obtain the missing information. Trials published in duplicate were included only once. Using the Dutch Cochrane Centre data form, the following information was captured:

- (1) characteristics of the trial (design, method of randomisation, withdrawals and dropouts, funding source);
- (2) trial participants (gender, age, wound characteristics, comorbidity, co-interventions);
- (3) intervention (SCS);
- (4) comparison intervention (non-surgical therapies);
- (5) primary outcome measure (limb salvage);
- (6) secondary outcome measures (pain relief, wound healing, quality of life, complications, costs, TcpO₂);
- (7) results.

Data analysis

Quantitative data were entered into the Cochrane RevMan 4.1 software and analysed using MetaView. For each trial and outcome, summary estimates of treatment effect (with 95% confidence intervals (CI)) were calculated for each comparison. For dichotomous outcomes the risk ratio (RR) and risk reduction (RD) were calculated (Deeks 1998). For continuous outcomes the mean difference (MD), or standardised mean difference (SMD), was used, where appropriate.

Analyses were performed for the studies, separately and combined. Stratification for the presence of diabetes mellitus could not be performed because too little information was given as to the

endpoints in diabetic patients. Results of clinically homogeneous trials (trials for which the participants, interventions, outcome measures, and timing of the follow-up measurements were considered to be similar enough) were combined using a fixed-effect model. A random-effects model was used in the case of statistical heterogeneity (assessed by visual inspection of the forest plots) and the availability of at least five studies. No pooling could be performed when an endpoint was addressed by only one study or when the study did not mention the standard deviations.

RESULTS

Description of studies

Nineteen reports were found on the basis of the inclusion criteria, nine of which were excluded. Of the nine excluded studies: four were excluded because they were not RCTs or CCTs (Claeys 1997b; Palombo 1995; Petrakis 2000; Tallis 1983). One reference was only a description of the study design (Klomp 1995), and one included reconstructable patients (Guarnera 1994). Three references were duplicate publications (Claeys 1997a; Claeys 1998b; Claeys 1999).

The resulting 10 papers, all published since 1994, described six trials. There were five national studies including: one Belgian (Suy 1994), one Swedish (Jivegard 1995), one German (Claeys 1996), and two Dutch studies (ESES; Spincemaille 2000a); and one international study, SCS-EPOS, (Amann 2003). Data were obtained for inclusion in the review. The study sizes varied from 37 to 120 patients, adding up to a total of 444 participating patients. Five out of the 10 papers (Klomp 1999; Klomp 2006; Spincemaille 2000b; Spincemaille 2000c; Ubbink 1999) focused on the Dutch ESES study (ESES), each addressing a different endpoint or aspect. In particular, Klomp (Klomp 1999), described overall limb salvage, ulcer healing, and costs; Klomp 2006 compared costs and effectiveness; Spincemaille (Spincemaille 2000b), focused on the effects on pain and quality of life; Spincemaille (Spincemaille 2000c) addressed the complications of SCS; and Ubbink (Ubbink 1999) described the effects on TcpO₂.

All studies included patients suffering from non-reconstructable critical leg ischaemia, that is having either ischaemic rest pain or ulcers smaller than 3 cm in diameter and on the basis of their clinical symptoms, peripheral blood pressure parameters and angiographic findings. The percentage of patients having only ischaemic rest pain ranged from 24% to 49% among the studies. In the German study (Claeys 1996) only patients with ischaemic ulcers were included; while in the Belgian study (Suy 1994) 11 patients with Buerger's disease were also enrolled. These 11 patients were excluded from the limb salvage meta-analysis.

In all studies, patients received control treatment with or without SCS. In the German study (Claeys 1996) and SCS-EPOS study (Amann 2003), a period of test stimulation was applied before definitive implantation of the SCS pulse generator. Control treatment consisted of optimum conservative treatment (local wound care, analgesics, anticoagulants, and antibiotics, if deemed necessary), which was comparable among the studies. In the German study (Claeys 1996) additional prostaglandin therapy was given to both groups.

In two studies, the transcutaneous oxygen (TcpO₂) measurements were used for patient classification. In the ESES study (ESES) a subgroup analysis was performed after classification of the patients

on the basis of their baseline TcpO₂ values. The SCS-EPOS study (Amann 2003) compared: patients treated with SCS who matched certain TcpO₂ and stimulation criteria; patients receiving SCS but not matching these criteria; and patients who received control treatment as SCS was regarded not to be a useful option, either on the basis of the initial TcpO₂ or an insufficient response to a period of test stimulation.

All studies used limb salvage (major amputation rate after 12 months) as the primary endpoint. Furthermore, in most studies pain relief and Fontaine stage (Fontaine 1954) were scored, and in some studies complications of SCS and quality of life were also noted.

Risk of bias in included studies

All studies were randomised trials except for the SCS-EPOS study (Amann 2003), which was a controlled clinical trial. This study refrained from randomisation in order to obtain sufficient patients for evaluation as it was anticipated from the experience of the previous studies that the number of eligible, non-reconstructable patients with chronic limb ischaemia would be limited. To pursue a randomised design would require a very long study duration, which was considered not to be feasible. Nevertheless, this study was included because it comprised the same target population, and the therapeutic decision making reflected the actual clinical situation.

Randomisation in the ESES study (ESES) was performed by means of a random numbers table via an independent randomisation institute. The other studies provided no specific allocation information. Sample size calculation was performed only in the Klomp (ESES) and SCS-EPOS (Amann 2003) studies.

Blinding of the treating physicians and patients was impossible due to the nature of the treatment, which is based on the correct location of the electrode so that the paraesthesiae (tingling sensation) induced by the electrical stimulation reaches the painful area. This prerequisite requires communication between physician and patient. The effect authors were, therefore, also not blinded.

In every study the groups were comparable at baseline as to the patients' demographic and risk factors. In most studies a considerable number of patients died during follow up. This was due to the fact that the studies included elderly patients who suffered from generalised atherosclerosis, which reduces life expectancy. Drop outs due to death during follow up were accounted for in all studies. The follow up on the remaining patients was (nearly) complete in all studies. In all RCTs an intention-to-treat analysis was performed. In the ESES study (ESES) an additional per protocol analysis was done because 13% of the patients received suboptimal stimulation.

Effects of interventions

Limb salvage

The Belgian (Suy 1994), Swedish (Jivegard 1995), German (Claeys 1996), ESES (ESES), and SCS-EPOS (Amann 2003) studies did not show a significant difference between groups in amputation frequency after 12, 18, or 24 months of follow up; although all studies showed a trend towards a better amputation-free salvage in the SCS group (for example Spincemaille 2000a: $P = 0.08$). This trend was stronger in a subgroup of patients selected by their initial TcpO₂ as compared to the overall result ($P = 0.17$ versus $P = 0.47$,

respectively) (Ubbink 1999). In the SCS-EPOS study (Amann 2003), the difference in cumulative limb salvage was significantly better in the patients treated with SCS ($P = 0.003$), and in particular in a subgroup selected based on their initial $TcpO_2$ and response to test stimulation ($P = 0.002$). In a subgroup of normotensive patients, the amputation rate after 18 months was lower in the SCS group ($P = 0.045$) (Jivegard 1995).

The baseline risk of amputation was about 50% in all studies (ranging from 46% to 64%), except in the Claeys study (Claeys 1996) in which it was 20%.

Pooling of the results yielded a significant effect of SCS after 12 months (RR 0.74, 95% CI 0.57 to 0.94; RD -0.11, 95% CI -0.20 to -0.02). This effect did not change substantially after exclusion of the single non-randomised SCS-EPOS study (Amann 2003) (RR 0.78, 95% CI 0.58 to 1.04; RD -0.09, 95% CI -0.19 to 0.01), or the Claeys study (Claeys 1996) which included only patients in Fontaine stage IV (RR 0.73, 95% CI 0.56 to 0.94; RD 0.13, 95% CI 0.02 to 0.23). This result means that nine patients need to be treated to prevent one more major amputation (NNT 9, 95% CI 5 to 50).

Pain relief

When judged with the visual analogue scale (VAS) (Carlsson 1983), pain relief was found to be significantly better in the SCS group after three months ($P = 0.0004$) (Spincemaille 2000a) and 12 months ($P < 0.01$) (Jivegard 1995). However, in the ESES study (Spincemaille 2000b) a highly significant reduction in pain scores (from a mean of 50 to 25) during follow up was found but with no difference between the two treatment groups.

The pain rating index (PRI), as part of the McGill pain questionnaire (Melzack 1975), also showed a significant decrease during follow up in both groups (Spincemaille 2000b). During follow up, patients receiving SCS used significantly less non-narcotic and narcotic analgesics than the patients treated conservatively (ESES; Spincemaille 2000b), as measured with the medication quantification scale (Masters-Steed 1992).

In patients who underwent a major amputation during the follow-up period, the VAS score declined significantly ($P < 0.001$) in both treatment groups. This held also for the PRI ($P = 0.001$). Thus, pain relief in amputated patients was substantially better than in non-amputated patients, irrespective of the treatment (Spincemaille 2000b).

Pooling could not be performed due to missing standard deviations.

Clinical improvement

In the studies of Claeys (Claeys 1996) and Suy (Suy 1994), the number of patients whose clinical stage improved from critical leg ischaemia to claudication was significantly higher in the SCS than in the conservative group ($P = 0.0014$) (Claeys 1996). When pooled, the RR was 4.9 (95% CI 2.0 to 11.9) and the RD 0.33 (95% CI 0.19 to 0.47). This means three patients have to be treated with SCS for one patient to reach Fontaine stage II (NNT 3, 95% CI 2 to 5).

Two studies reported on the healing of ischaemic ulcers (Claeys 1996; ESES). Claeys found SCS had a significantly better effect on wound healing than conservative treatment ($P = 0.013$), whereas

Klomp (ESES) found no significant difference. Pooling resulted in no significant difference between the two treatment modalities.

When subgroups of patients with and without hypertension were compared for ulcer healing, Claeys (Claeys 1996) found a significantly better effect of SCS than conservative treatment in normotensives, whereas Suy (Suy 1994) found a better SCS effect in hypertensives.

No significant differences in treatment effects were found between diabetic and non-diabetic patients (Claeys 1996; ESES).

Ankle brachial pressure index (ABPI)

The study of Claeys (Claeys 1996) showed a significant difference in ABPI change during follow up: 0.03, an increase of 10% compared to baseline in the SCS group; and -0.058, a decrease of 17% compared to baseline in the conservative treatment group ($P < 0.02$). Only SCS patients who achieved complete ulcer healing showed a significant ABPI increase of 0.09 ($P < 0.01$). However, Jivegard (Jivegard 1995) found no change in ABPI in either groups during treatment. Pooling could not be performed due to missing standard deviations.

Quality of life

In the SCS-EPOS study (Amann 2003) an SF-12 questionnaire was used during follow up only for the SCS-treated patients. This showed no worsening of the overall quality of life.

The ESES study (ESES), described by Spincemaille (Spincemaille 2000b), applied the Nottingham health profile (NHP) and the Euroqol in both treatment groups. The overall score of the NHP decreased (that is quality of life improved) during follow up in both treatment groups. The mobility score of the NHP was significantly better in the patients treated with SCS ($P < 0.01$). In case of an amputation, mobility was reduced and not influenced by rehabilitation programmes. The Euroqol also showed an improvement after 12 months, in the SCS and conservative groups (SCS: from 54 to 11; conservative: from 51 to 10). After amputation these scores worsened to 66 and 61, respectively, but recovered over a period of several months to reach similar values to those of non-amputated patients.

Local transcutaneous oxygen tension ($TcpO_2$)

In the Claeys study (Claeys 1996) the $TcpO_2$ (measured with a Hellige device), which was comparable at baseline (SCS: 10 mm Hg, conservative: 12 mm Hg), was significantly higher in the SCS group after 12 months of treatment (21 mm Hg versus 11 mm Hg; $P < 0.001$).

In the ESES study (Ubbink 1999) $TcpO_2$ (using a radiometer device) was similar at baseline (10 mm Hg in both groups) and increased significantly ($P < 0.05$) during follow up, but was not significantly different between groups. This was found carrying forward the results before amputation.

Only the mean $TcpO_2$ results after 12 months could be pooled. Using a random-effects model, no significant difference could be detected.

Complications

No differences in mortality were observed. Usually only the complications of SCS treatment were mentioned. In the ESES study (ESES) side effects of medical treatment in the conservative group

were upper gastrointestinal bleeding (three), nausea (seven), and dizziness (two); while in the SCS group duodenal perforation (one), nausea (two), and pruritus (itching) (one) were recorded.

Initial implantation problems (technical or anatomical problems causing failure of positioning the electrode in the epidural space) were recorded in two trials. In the SCS-EPOS study (Amann 2003) two out of a total of 75 patients could not have electrodes implanted. In the ESES study (Spincemaille 2000c) this was nine out of 60 patients. After pooling, the risk of implantation problems was 8% (random-effects model: 95% CI -6 to 22%), implying that in every 12 patients an implantation problem could be expected.

All trials reported the number of changes in stimulation requiring a surgical re-intervention, which could be because of dislocation of the electrode or fracture of the lead. Multicentre trials showed the highest complication incidence. Pooling resulted in a risk of 12% (random-effects model: 95% CI 5 to 20%). Infections of the lead or subcutaneous pulse generator pocket occurred less frequently. The pooled risk from the six studies was 3% (95% CI 0 to 6%). Depletion of the battery within 18 months of follow up also occurred: in five patients in the SCS-EPOS study (Amann 2003), and in three patients in the ESES study (Spincemaille 2000c).

The overall number of complications of SCS treatment (comprising infection of lead or impulse generator pocket, dislocation or breakage of the lead, and early depletion of the battery) were pooled over the six trials. The overall complication risk was 0.18 (random-effects model: 95% CI 0.03 to 0.32), indicating a number needed to harm of 6 (95% CI 3 to 33).

Costs

Only the ESES study (ESES) included a cost comparison (see Table 1). The average overall costs of hospitalisation, rehabilitation, operative procedures, stimulator, outpatient care, professional home care, medication and non-medical costs at two years were EUR 36,500 in the SCS group and EUR 28,600 in the conservative group. This was a significant difference ($P < 0.009$). After adjustment for mortality these figures were EUR 31,340 (SCS) and EUR 23,780 (conservative) ($P < 0.002$).

DISCUSSION

As compared with the large total number of publications on SCS for non-reconstructable critical leg ischaemia (CLI), only a few randomised studies have been performed. One of the reasons may be the limited number of patients with CLI regarded as non-reconstructable, and thus considered eligible candidates for such a trial, a fact illustrated by the relatively small study sizes of randomised studies. The chance of publication bias is regarded as small, considering that the manufacturers of nearly all SCS devices are keeping track of all studies that are or have been performed on SCS in this patient group.

Due to the non-blinded character of the studies, limb salvage results could be biased if amputations were postponed in SCS-treated patients. However, progressive necrosis (localised tissue death) with imminent sepsis (infection) and intractable pain despite maximum analgesic therapy (which was allowed in both treatment groups) were the absolute indications for an amputation. Hence, it is not likely this has had a significant influence on eventual limb salvage.

The ongoing discussion about the definition of critical leg ischaemia and non-reconstructability further obscures the indication for such a therapy. Furthermore, this patient group has a limited life expectancy due to their increased age and the presence of generalised atherosclerosis, which limits the benefit of any treatment. On the other hand, this patient group faces the ultimate prospect of amputation. Hence, any alternative treatment option with a limb saving and pain relieving potential deserves proper evaluation.

The included trials all focused on limb salvage, clinical improvement, and complications, comparing SCS with optimum non-surgical therapy. Only a few studies addressed quality of life and cost. Although blinding was impossible, the overall quality of the studies was good. The results of some (secondary) endpoints (for example ABPI, $TcpO_2$) are difficult to interpret as they are influenced by the loss from the trial of patients undergoing an amputation during follow up, which leaves only the 'better' patients. This positively biases the results.

None of the individual RCTs revealed a significant beneficial effect on limb salvage. Probably the individual studies, which took approximately five years for each to be completed, tended to be underpowered. To include a larger number of patients that matched the strict inclusion criteria would have taken too much time. However, after pooling a positive effect on limb salvage was found at the cost of a significantly higher number of (correctable) complications and (probably) higher costs. Additionally, there is some evidence of a beneficial effect on ulcer healing and pain relief. The finding that $TcpO_2$, but not ABPI, seems to increase during follow up suggests SCS treatment mainly acts on the local microcirculation. Pain relief and ulcer healing may also improve walking ability, which may further enhance local circulation.

The general quality of life seemed to remain unchanged. Apparently this is influenced by other major factors in life, or the questionnaires used are too insensitive to measure specific changes due to the treatment of CLI. To date, we are still in want of specific questionnaires to appreciate quality of life in CLI. A major amputation can still be considered as an alternative treatment because it leads to good pain relief, albeit at the cost of a (temporary) reduction in mobility.

AUTHORS' CONCLUSIONS

Implications for practice

There is evidence that SCS is better than conservative treatment alone in order to achieve amputation risk reduction, pain relief, and improvement of the clinical situation in patients with non-reconstructable chronic stable critical limb ischaemia. The effect of SCS appears to be stronger after further patient selection on the basis of a beneficial local transcutaneous oxygen tension ($TcpO_2$) and test stimulation period. This beneficial effect should be weighed against the harm SCS may cause (implantation failures and relatively mild complications). In addition, the impact of SCS treatment on healthcare budgets needs to be considered.

If pain relief is the primary goal, a major amputation may be the treatment of choice in patients with an already limited mobility.

The higher complication rate, as found in multicentre studies enrolling few patients per centre, indicates that this treatment

should be reserved to specialised centres which have the facilities and expertise to provide SCS.

Implications for research

Given the present evidence, SCS treatment appears beneficial to a small subgroup of CLI patients. Despite the expected low inclusion rates, randomised controlled trials with clear inclusion criteria may further elucidate which patients may benefit from SCS therapy. Quality of life, cost-effectiveness, and pain assessment in patients after an amputation should be among the endpoints. To assess the quality of life, the SF36 (Ware 1998) is recommended as the best validated general questionnaire while still in want of a specific questionnaire for CLI.

Inclusion criteria should aim at including patients who are most likely to benefit from SCS treatment. A period of test stimulation and TcpO₂ monitoring to assess the local circulation appear useful for this purpose. Further research is required in this area. Usually effect parameters such as the TcpO₂ are calculated during

follow up without carrying forward the data obtained from those who previously underwent an amputation. This leaves only the participants who retained their leg and probably had better oxygenation. This bias should be avoided.

Given the evidence that limb salvage obtained with SCS is comparable to (distal) bypass surgery, other indications for experimental SCS treatment may also be considered (for example reconstructable CLI) and compared with less promising surgical interventions such as very distal or infrainguinal prosthetic bypass procedures.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Amann 2003

Methods	Controlled clinical trial.
Participants	Country: 17 European centres. Number of participants: 112. Age: SCS group = 68 ± 13 SD; Control group = 67 ± 9 SD. Sex: M=75; F=37. Inclusion criteria: Non-reconstructable CLI. Fontaine stages III; persistent pain at rest > 2 weeks or ischaemic skin lesions. Exclusion criteria: Extensive necrosis; infected gangrene; terminally ill.

Amann 2003 (Continued)

Interventions	Treatment group: SCS + best medical therapy (n=73). Control group: Best medical therapy (n=39). Duration: 18 months follow up.
Outcomes	Limb survival, pain relief, QoL, Fontaine stage, complications.
Notes	TcpO ₂ selection. Test stimulation. Raw data available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	D - Not used

Claeys 1996

Methods	Randomised controlled trial.
Participants	Country: Germany. Number of participants: 86. Age: SCS group = 67.7 ± 11.9 SD; Control group = 69.9 ± 10.2 SD. Sex: M=49; F=37. Inclusion criteria: Non-reconstructable CLI; Fontaine stage IV; ulcers or gangrene present for minimum of 3 weeks; ankle pressure < 50mmHg. Exclusion criteria: Mixed type of ulceration; local infection; patients suitable for reconstructive procedures.
Interventions	Treatment group: SCS + PGE1 (n=45). Control group: Conservative medical therapy - PGE1 (n=41). Duration: 1 year follow up.
Outcomes	Limb survival, pain relief, ABPI, Fontaine stage, ulcer healing, complications.
Notes	TcpO ₂ . Test stimulation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

ESES

Methods	Randomised controlled trial. Randomisation by random-numbers table, stratified by diabetes, ankle pressure, and hospital. Treatment allocation performed in an independent institute.
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Spinal cord stimulation for non-reconstructable chronic critical leg ischaemia (Review)

ESES (Continued)

Participants	Country: The Netherlands, 17 centres. Number of participants: 120. Age: SCS group = 73.1 ± 9.8 SD; Control group = 721.1 ± 10.6 SD. Sex: M=70; F=50. Inclusion criteria: Non-reconstructable CLI, persistent pain at rest > 2 weeks or ischaemic skin lesions, ankle systolic pressure < 50mmHg. Exclusion criteria: Extensive necrosis, infected gangrene, terminally ill.
Interventions	Treatment group: SCS + best medical therapy (n=60). Control group: Best medical therapy (n=60). Duration: 2 years.
Outcomes	Limb survival, pain relief, Fontaine stage, QoL, ABPI complications.
Notes	TcpO ₂ selection. Raw data available in Ubbink 1999b reference.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Jivegard 1995

Methods	Randomised controlled trial. Method of randomisation: unsure.
Participants	Country: Sweden, 2 university hospitals. Number of participants: 51. Age: SCS group = 73 ± 12 SD; Control group = 73 ± 12 SD. Inclusion criteria: Severe chronic (> 2 weeks duration) lower limb ischaemia. non-reconstructable CLI. Exclusion criteria: Rapidly progressing ischaemia, gangrene of more than one toe, extensive infection and/or non-healing ischaemic ulcerations.
Interventions	Treatment group: SCS + oral analgesics (n=25). Control group: Oral analgesic (n=26). Duration: 18 months follow up.
Outcomes	Limb survival, pain relief, ABPI, toe pressure, complications.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Spincemaille 2000a

Methods	Randomised controlled trial (preliminary results).
Participants	Country: The Netherlands. Number of participants: 37. Age: SCS group: 72; Control group: 70. Range: 56 to 87. Sex: M=28; F=9. Inclusion criteria: Non-reconstructable CLI; persistent pain at rest, or ischaemic skin lesions. Exclusion criteria: infected gangrene, terminally ill, ulcer surface > 3 cm.
Interventions	Treatment group: SCS+ best medical therapy (n=19). Control group: Best medical therapy: analgesic and vasoactive drugs (n=18). Duration: 2 years.
Outcomes	Limb survival, pain relief.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Suy 1994

Methods	Randomised controlled trial.
Participants	Country: Belgium, 3 university hospitals. Number of participants: 38. Age: SCS group 66 ± 11 SD; Control group 65 ± 9 SD. Inclusion criteria: chronic ischaemic pain related to PAOD; non-reconstructable CLI (n=27) and Buerger (n=11 excluded).
Interventions	Treatment group: SCS (n=20). Control group: Conservative therapy (n=18). Duration: follow up 20 ± 15 months.
Outcomes	Limb survival, pain relief, Fontaine stage, complications.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

ABPI: Ankle Brachial Pressure Index

Hg: Mercury

CLI: Critical limb ischaemia

PGE1: Prostaglandin E1

QoL: Quality of life

SCS: Spinal cord stimulation

TcpO₂: Transcutaneous oxygen pressure

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Claeys 1997a	Double publication.
Claeys 1997b	No controls.
Claeys 1998b	Double publication.
Claeys 1999	Double publication.
Guarnera 1994	Inclusion of reconstructable CLI patients.
Palombo 1995	No controls.
Petrakis 2000	No controls.
Tallis 1983	No controls.

DATA AND ANALYSES

Comparison 1. Limb survival

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Amputations (12 months)	6	433	Risk Difference (M-H, Fixed, 95% CI)	-0.11 [-0.20, -0.02]
2 Amputation rate in non-hypertensives (18 months)	1		Risk Difference (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Limb survival, Outcome 1 Amputations (12 months).

Study or subgroup	SCS n/N	Conservative n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
Amann 2003	21/73	18/39		24.12%	-0.17[-0.36,0.01]
Claeys 1996	7/45	8/41		20.36%	-0.04[-0.2,0.12]
ESES	24/60	29/60		28.47%	-0.08[-0.26,0.09]
Jivegard 1995	9/25	13/26		12.09%	-0.14[-0.41,0.13]
Spincemaille 2000a	6/19	9/18		8.77%	-0.18[-0.5,0.13]
Suy 1994	5/16	4/11		6.19%	-0.05[-0.41,0.31]
			-1 -0.5 0 0.5 1	Favors SCS Favors control

Analysis 1.2. Comparison 1 Limb survival, Outcome 2 Amputation rate in non-hypertensives (18 months).

Comparison 2. Pain relief

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in VAS score (0-100; where 100 is worst) after 12 months	2	166	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Change in Pain Rating Index (overall; where higher is worse) after 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Change in VAS score (0-100; where 100 is worst) after 3 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 Pain relief, Outcome 1 Change in VAS score (0-100; where 100 is worst) after 12 months.

Analysis 2.2. Comparison 2 Pain relief, Outcome 2 Change in Pain Rating Index (overall; where higher is worse) after 12 months.

Study or subgroup	SCS		Control		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
ESES	60	-11.5 (0)	60	-13 (0)		Not estimable
					Favours treatment -10 -5 0 5 10 Favours control	

Analysis 2.3. Comparison 2 Pain relief, Outcome 3 Change in VAS score (0-100; where 100 is worst) after 3 months.

Study or subgroup	SCS		Control		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Spincemaille 2000a	19	4.7 (0)	18	1.5 (0)		Not estimable
					Favours treatment -10 -5 0 5 10 Favours control	

Comparison 3. Clinical improvement

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Reaching Fontaine stage II	2	124	Risk Difference (M-H, Fixed, 95% CI)	0.33 [0.19, 0.47]
2 Reaching Fontaine stage III	2	206	Risk Difference (M-H, Random, 95% CI)	0.07 [-0.24, 0.38]
3 Ulcer healing and hypertension	2	72	Risk Difference (M-H, Fixed, 95% CI)	-0.54 [-0.73, -0.35]
3.1 Hypertensives	1	44	Risk Difference (M-H, Fixed, 95% CI)	-0.57 [-0.80, -0.33]
3.2 Non-hypertensives	1	28	Risk Difference (M-H, Fixed, 95% CI)	-0.5 [-0.82, -0.18]

Analysis 3.1. Comparison 3 Clinical improvement, Outcome 1 Reaching Fontaine stage II.

Study or subgroup	SCS	Control	Risk Difference		Weight	Risk Difference
	n/N	n/N	M-H, Fixed, 95% CI			M-H, Fixed, 95% CI
Claeys 1996	18/45	4/41			69.37%	0.3[0.13,0.47]
Suy 1994	9/20	1/18			30.63%	0.39[0.15,0.64]
Total (95% CI)	65	59			100%	0.33[0.19,0.47]
Total events: 27 (SCS), 5 (Control)						
Heterogeneity: Tau²=0; Chi²=0.37, df=1(P=0.54); I²=0%						
Test for overall effect: Z=4.66(P<0.0001)						
			Favours control -1 -0.5 0 0.5 1 Favours SCS			

Analysis 3.2. Comparison 3 Clinical improvement, Outcome 2 Reaching Fontaine stage III.

Analysis 3.3. Comparison 3 Clinical improvement, Outcome 3 Ulcer healing and hypertension.

Comparison 4. Ankle/brachial index

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Ankle/brachial pressure index increase after 12 months	2	137	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 4.1. Comparison 4 Ankle/brachial index, Outcome 1 Ankle/brachial pressure index increase after 12 months.

Study or subgroup	SCS		Control		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Claeys 1996	45	0 (0)	41	-0.6 (0)			Not estimable
Jivegard 1995	25	-0 (0)	26	0 (0)			Not estimable
Total ***	70		67				Not estimable
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							

Favours treatment -10 -5 0 5 10 Favours control

Comparison 5. Quality of life

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Nottingham Health Profile (0-100; where 100 is worst) after 12 months	1	189	Mean Difference (IV, Fixed, 95% CI)	1.0 [-0.20, 2.20]
1.1 Mobility score amputees	1	52	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Overall	1	85	Mean Difference (IV, Fixed, 95% CI)	1.0 [-0.20, 2.20]
1.3 Mobility score non-amputees	1	52	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Euroqol (0-100; where 100 is worst) after 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 5.1. Comparison 5 Quality of life, Outcome 1 Nottingham Health Profile (0-100; where 100 is worst) after 12 months.

Study or subgroup	SCS		Control		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
5.1.1 Mobility score amputees							
ESES	29	61.2 (0)	23	57 (0)			Not estimable
Subtotal ***	29		23				Not estimable
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
5.1.2 Overall							
ESES	44	35 (2.6)	41	34 (3)		100%	1[-0.2,2.2]
Subtotal ***	44		41			100%	1[-0.2,2.2]
Heterogeneity: Not applicable							
Test for overall effect: Z=1.64(P=0.1)							
5.1.3 Mobility score non-amputees							

Favours treatment -4 -2 0 2 4 Favours control

Analysis 5.2. Comparison 5 Quality of life, Outcome 2 Euroqol (0-100; where 100 is worst) after 12 months.

Comparison 6. TcpO2

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 TcpO2 after 12 months	2	197	Mean Difference (IV, Random, 95% CI)	1.39 [-15.66, 18.44]

Analysis 6.1. Comparison 6 TcpO2, Outcome 1 TcpO2 after 12 months.

Comparison 7. Complications

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in stimulation requiring re-intervention (within 12 months)	6	412	Risk Difference (M-H, Random, 95% CI)	0.12 [0.04, 0.20]
2 Infection requiring removal	6	412	Risk Difference (M-H, Fixed, 95% CI)	0.03 [-0.00, 0.06]
3 Battery: end of life	6	412	Risk Difference (M-H, Fixed, 95% CI)	0.04 [0.00, 0.07]
4 Overall complications requiring re-intervention	5	375	Risk Difference (M-H, Random, 95% CI)	0.18 [0.03, 0.33]
5 Initial implantation problems (not included in overall complications)	2	232	Risk Difference (M-H, Random, 95% CI)	0.08 [-0.06, 0.23]

Analysis 7.1. Comparison 7 Complications, Outcome 1 Change in stimulation requiring reintervention (within 12 months).

Analysis 7.2. Comparison 7 Complications, Outcome 2 Infection requiring removal.

Analysis 7.3. Comparison 7 Complications, Outcome 3 Battery: end of life.

Analysis 7.4. Comparison 7 Complications, Outcome 4 Overall complications requiring re-intervention.

Analysis 7.5. Comparison 7 Complications, Outcome 5 Initial implantation problems (not included in overall complications).

ADDITIONAL TABLES

Table 1. Costs

Costs (Euros)	SCS (Euros)	Conservative (Euros)
Hospitalisation	11,779	12,321
Rehabilitation	6748	7471
Operative procedures	8362	417
Stimulator implant	7215	0
Professional home care	Equal	Equal
Outpatient costs	Negligible	Negligible
Medication	Negligible	Negligible
Non-medical	Negligible	Negligible
TOTAL	36,502	28,617

APPENDICES

Appendix 1. CENTRAL search strategy

#1	MeSH descriptor: [Arteriosclerosis] this term only	890
#2	MeSH descriptor: [Arteriolosclerosis] this term only	0
#3	MeSH descriptor: [Arteriosclerosis Obliterans] this term only	71
#4	MeSH descriptor: [Atherosclerosis] this term only	382
#5	MeSH descriptor: [Arterial Occlusive Diseases] this term only	753
#6	MeSH descriptor: [Intermittent Claudication] this term only	710

(Continued)

#7	MeSH descriptor: [Ischemia] this term only	751
#8	MeSH descriptor: [Peripheral Vascular Diseases] explode all trees	2146
#9	MeSH descriptor: [Vascular Diseases] this term only	379
#10	MeSH descriptor: [Leg] explode all trees and with qualifiers: [Blood supply - BS]	1069
#11	MeSH descriptor: [Femoral Artery] explode all trees	719
#12	MeSH descriptor: [Popliteal Artery] explode all trees	250
#13	MeSH descriptor: [Iliac Artery] explode all trees	151
#14	MeSH descriptor: [Tibial Arteries] explode all trees	29
#15	(atherosclero* or arteriosclero* or PVD or PAOD or PAD)	16775
#16	(arter*) near (*occlus* or steno* or obstruct* or lesio* or block* or obliter*)	4842
#17	(vascular) near (*occlus* or steno* or obstruct* or lesio* or block* or obliter*)	1368
#18	(vein*) near (*occlus* or steno* or obstruct* or lesio* or block* or obliter*)	706
#19	(veno*) near (*occlus* or steno* or obstruct* or lesio* or block* or obliter*)	974
#20	(peripher*) near (*occlus* or steno* or obstruct* or lesio* or block* or obliter*)	1352
#21	peripheral near/3 dis*	3203
#22	arteriopathic	9
#23	(claudic* or hinken*)	1427
#24	(isch* or CLI)	16663
#25	dysvascular*	13
#26	leg near/4 (obstruct* or occlus* or steno* or block* or obliter*)	176
#27	limb near/4 (obstruct* or occlus* or steno* or block* or obliter*)	227
#28	(lower near/3 extrem*) near/4 (obstruct* or occlus* or steno* or block* or obliter*)	136
#29	(aort* or iliac or femoral or popliteal or femoro* or fempop* or crural) near/3 (obstruct* or occlus*)	324
#30	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29	39111
#31	MeSH descriptor: [Electric Stimulation Therapy] explode all trees	4045
#32	spin* near stimulat*	388
#33	column* near stimulat*	11

(Continued)

#34	epidur* near stimulat*	79
#35	MeSH descriptor: [Electric Stimulation] explode all trees	1460
#36	#31 or #32 or #33 or #34 or #35	5657
#37	#30 and #36 in Trials	427

Appendix 2. Keywords used in search strategy

Spinal cord stimulation
Dorsal column stimulation
Epidural spinal stimulation
Epidural electrical stimulation

Critical limb isch(a)emia
Lower limb isch(a)emia
Leg isch(a)emia
Peripheral vascular disease
Peripheral arterial (occlusive) disease
Atherosclerosis

Non-reconstructable
Intractable
Inoperable

Limb salvage
Amputation
Pain relief
Wound / ulcer healing
Quality of life
Complications
Cost

FEEDBACK

Klomp, October 2004

Summary

22 October 2004

This review [1] was recently published as well in the British Journal of Surgery [2], but contains major problems. The review describes 6 studies, with patient numbers varying from 27 to 120 patients. One (randomised) study was never reviewed (Suy), one study was NOT randomised (Amann), one study was stopped prematurely (Spincemaille), and for at least three studies concealment of treatment allocation was dubious. The selected data for the "amputation rate after 12 months" are incorrect for our study [3], and the use of data from a subgroup in the smallest study (Suy) is unjustifiable.

At least the choices made in the process should be adequately described. Presently, the debatable choices of data input (non-randomised data, subgroup-data) are not properly addressed in the methodological or discussion sections.

The same meta-analysis, performed with the, in our view proper amputation data input of 5 randomised studies, generates a risk difference of -0.07 (95% CI: -0.17 to +0.03) instead of -0.13 (95% CI: -0.22 to -0.04). The main conclusion, that spinal cord stimulation is better than conservative treatment alone in achieving a reduction in amputation risk, is not justified. If SCS is beneficial, the magnitude of the effect is very small.

We think that the issues are of such relevance that they should at least be available to users of the Cochrane library who read the Ubbink review of SCS treatment. So modifications are required in the present Cochrane review [4,5].

Houke Klomp, Amsterdam
Ewout Steyerberg, Rotterdam

References

- 1.Ubbink DT, Vermeulen H. Spinal cord stimulation for non-reconstructable chronic critical leg ischaemia. *Cochrane Database Syst Rev.* 2003;CD004001.
- 2.Ubbink DT, Vermeulen H, Spincemaille GH, Gersbach PA, Berg P, Amann W. Systematic review and meta-analysis of controlled trials assessing spinal cord stimulation for inoperable critical leg ischaemia. *Br J Surg.* 2004;91:948-55.
- 3.Klomp HM, Spincemaille GH, Steyerberg EW, Habbema JD, van Urk H. Spinal-cord stimulation in critical limb ischaemia: a randomised trial. ESES Study Group. *Lancet.* 1999;353:1040-4.
- 4.Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *Jama.* 1995;273:408-12.
- 5.Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, Tugwell P, Klassen TP. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet.* 1998;352:609-13.

Reply

4 November 2004

We do not agree with the comment that our review would contain major problems and improper descriptions of our methodology for the following reasons:

- 1.The methodological quality and validity of every trial was judged according to standards supplied by the Dutch Cochrane Centre (while DU was replaced as author when judging trials of which he was co-author). This implies that even the non-peer-reviewed paper by Suy et al. was methodologically checked by independent authors. This has also been mentioned in the 'Methods of the review' section.
- 2.The trials we included in our study were defined beforehand, as stated in the 'Criteria For Considering Studies For This Review', under 'Types of studies', which comprised controlled clinical trials, including the motivation for this. Because we are aware of the possible effects of including non-randomised data, we have conducted a sensitivity analysis, as mentioned in the Results section under 'Limb salvage': Excluding this trial (Amann study) did not influence the results substantially. The Spincemaille study stopped prematurely, probably because the Dutch multicenter study was about to start, which they joined. This is no reason for excluding the study from our meta-analysis.
- 3.We have checked with the commenter the data regarding the ESES trial she disagreed with. Instead of the 27 versus 32 amputations at 12 months we present, she mentioned 24 versus 29 amputations, which was not apparent from the Lancet paper. We repeated the meta-analysis with these data and found that this does not alter the results, but we will correct these data in the next update of our review.
- 4.The smallest trial by Suy et al. included patients with non-reconstructable critical leg ischaemia as well as Buerger's disease. In order not to compromise homogeneity of the patients in this meta-analysis, only CLI patients were included, which has been addressed in the 'Description of studies' section. Again, we re-analysed the data after excluding these (few) data from the meta-analysis. This did not influence limb salvage risk difference significantly.
- 5.The same meta-analysis, performed with the adapted amputation data from six controlled trials generates a risk difference of -0.11 (95% CI: -0.20 to -0.02).
- 6.In general, systematic reviews offer the highest level of evidence available, even if not all available studies confirm concealment of allocation. This evidence supports the beneficial effect of SCS. We agree that the magnitude of this effect may appear small, but to us, a risk difference of around 10% as to major amputations within one year seems clinically relevant. Even if the confidence interval would cross zero, one should be careful to conclude there is no effect (Alderson P, Chalmers I. Survey of claims of no effect in abstracts of Cochrane reviews. *BMJ.* 2003; 326(7387): 475).

Dirk Ubbink and Hester Vermeulen, November 2004.

Contributors

Comments by:

Houke Klomp, Amsterdam and Ewout Steyerberg, Rotterdam

Response to comments by:

Dirk Ubbink and Hester Vermeulen, Amsterdam

WHAT'S NEW

Date	Event	Description
26 February 2013	Review declared as stable	This Cochrane review has been marked stable and will only be updated when new studies are identified.

HISTORY

Protocol first published: Issue 1, 2003

Review first published: Issue 3, 2003

Date	Event	Description
17 January 2013	New citation required but conclusions have not changed	Searches re-run but no new studies identified. Review search dates updated, minor copy edits made to text. Conclusions not changed.
17 January 2013	New search has been performed	Searches re-run but no new studies identified. Review search dates updated.
24 September 2008	New search has been performed	Searches re-run and no new studies found. One additional report (Klomp 2006) added to ESES study. Correction made to the analysis results reported in the last paragraph of "Effects of Interventions", Limb salvage. Plain language summary added.
8 July 2008	Amended	Converted to new review format.
24 June 2005	New citation required but conclusions have not changed	No new trials found at last search. Review updated with minor formatting changes and correction to the numbers of amputations in the ESES trial, in accordance with the Comment submitted by Klomp and Steyerberg.
16 November 2004	Amended	Synopsis added.
4 November 2004	Feedback has been incorporated	Feedback and response to feedback added.

CONTRIBUTIONS OF AUTHORS

DU identified potentially relevant papers, decided upon eligibility and quality of trials, extracted data, and wrote the review.

HV identified potentially relevant papers, discussed their eligibility with DU, decided upon the quality of trials, and extracted data.

DECLARATIONS OF INTEREST

Bakken Research Centre sponsored the principal investigator (DU) as 'quality officer' for the duration of the Spinal Cord Stimulation European Peripheral Artery Disease Outcomes Study (SCS-EPOS). The Research Centre belongs to the Medtronic Company, which is the worldwide manufacturer of the neurostimulators for SCS treatment. Medtronic did not, however, sponsor the preparation of this review.

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Internal sources

- No sources of support supplied

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INDEX TERMS**Medical Subject Headings (MeSH)**

Amputation; Chronic Disease; Controlled Clinical Trials as Topic; Ischemia [*therapy]; Leg [*blood supply]; Limb Salvage [methods]; Randomized Controlled Trials as Topic; Spinal Cord Stimulation [adverse effects] [*methods]

MeSH check words

Humans