Spinal cord stimulation in the treatment of refractory angina: systematic review and meta-analysis of randomised controlled trials

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CRD summary
The authors concluded spinal cord stimulation appeared to be effective and safe in the management of refractory angina, and of similar efficacy and safety to percutaneous myocardial laser revascularisation. Given that the authors found either no statistically significant difference between the intervention and inactive comparator, or a statistically significant moderate effect size, the authors' conclusions overstate the evidence presented.

Authors' objectives
To determine the efficacy, safety and cost effectiveness of spinal cord stimulation in the treatment of refractory angina.

Searching
MEDLINE, MEDLINE In Process and other non-indexed citations, EMBASE, and the Cochrane Library were searched, without language restriction, up to 2008. Search terms were reported. The metaRegister of Controlled Trials, ClinicalTrials.gov and websites of national and international health technology assessment organisations, the US Food and Drug Administration and the European Medicines Agency were searched. Experts in the field were contacted.

Study selection
Eligible for inclusion in the review were parallel or crossover randomised controlled trials (RCTs) of spinal cord stimulation (either alone or in combination with other treatment) in patients with refractory angina.

There were three main outcome categories: efficacy including exercise capacity, ischaemic burden (combined frequency and severity of ischaemic changes during ambulatory electrocardiogram/ECG monitoring), anti-angina drug consumption, functional class and health-related quality of life; safety including mortality, morbidity, and spinal cord stimulation related complications; and healthcare utilisation or costs.

All the included trials were conducted in Europe. Participants consisted of patients that had refractory angina (in spite of optimal medical therapy) and who were unable to undergo revascularisation. Included patients had angina of New York Heart Association (NYHA) class III and IV or Canadian Cardiovascular Society (CCS) class 3 or 4. The mean age of patients ranged from 59 to 76 years, and were predominately male (range 56 to 88%). Active comparators were patients who underwent coronary artery bypass grafting or percutaneous myocardial laser revascularisation. Inactive comparators were patients who did not receive a spinal cord stimulation implantation or patients who received an inactive spinal cord stimulation implantation.

Two reviewers performed study selection.

Assessment of study quality
Trial quality was assessed using the following criteria: method of randomisation, allocation concealment, blinding, reporting of loss to follow-up/drop-out, and use of intention-to-treat analysis. The modified Jadad scale (randomisation, double blinding, withdrawals/drop-outs), with a maximum score of 5, was also used.

Two reviewers independently performed study quality assessment.

Data extraction
Data were extracted into a standardised data form. Means and standard deviations were used to calculate standardised mean differences (SMDs) and 95% confidence intervals (CIs), and number of patient adverse events. Data were extracted for all follow-up times reported. Trial authors were contacted for missing data.

Two reviewers independently performed data extraction.
Methods of synthesis
For each trial, within group differences (outcome at follow-up compared with baseline) and between group differences (unclear if this was the difference in outcome at follow-up or difference in change from baseline between groups), for the direction of treatment effect and statistical significance, were presented in a table. Data for adverse events were also presented in a table. Data for functional class were presented in a narrative form.

For the remaining outcomes, standardised mean differences were combined in a meta-analysis using a random-effects (DerSimonian-Laird) model. For crossover trials, only data from the first treatment period were included in the analysis.

Heterogeneity was assessed using the $X^2$ and $I^2$ tests.

Publication bias was assessed using funnel plots.

Results of the review
Seven RCTs were included in the review (n=270 patients, sample size ranged from 22 to 104). Follow-up ranged from 48 hours to five years. Trial quality ranged from 2 to 4 on the Jadad scale, with a median score of 2.

Exercise capacity: There was no statistically significant difference in exercise capacity between spinal cord stimulation and coronary artery bypass grafting (one RCT), or between spinal cord stimulation and percutaneous myocardial laser revascularisation (one RCT). Spinal cord stimulation was associated with statistically significant greater exercise capacity compared to inactive comparators (SMD 0.76, 95% CI: 0.07 to 1.46; four RCTs). However, there was evidence of statistically significant heterogeneity ($I^2=60\%$).

Ischaemic burden: There was no statistically significant difference in ischaemic burden between spinal cord stimulation and active comparator (one RCT), or between spinal cord stimulation and inactive comparator (three RCTs).

Nitrate consumption: There was no statistically significant difference in nitrate consumption between spinal cord stimulation and active comparator (one RCT), or between spinal cord stimulation and inactive comparator (three RCTs). However, for the comparison between spinal cord stimulation and inactive comparator, there was evidence of statistically significant heterogeneity ($I^2=74\%$).

Health-related quality of life: There was no statistically significant difference in health-related quality of life between spinal cord stimulation and coronary artery bypass grafting (one RCT), or between spinal cord stimulation and percutaneous myocardial laser revascularisation (one RCT). Spinal cord stimulation was associated with a statistically significant greater quality of life than inactive comparator (SMD 0.836, 95% CI 0.32 to 1.34; three RCTs).

Adverse events: Adverse events included infections (one out of 104 patients; three RCTs), lead migration/fracture (10 out of 128 patients; four RCTs). Risk of non-fatal events, fatal events appeared similar for spinal cord stimulation to that of percutaneous myocardial laser revascularisation (one RCT). However, compared with spinal cord stimulation, coronary artery bypass grafting was associated with a statistically significant greater incidence of total mortality at six months (one out of 53 patients versus seven out of 51 patients; p=0.02).

Cost information
One trial reported health care utilisation and costs, which were at two years follow-up. Spinal cord stimulation was associated with a statistically significant shorter mean stay in hospital (mean 5.0 days) compared with coronary artery bypass grafting (mean 11.1 days; p<0.0001). Spinal cord stimulation was associated with a statistically significant lower average costs (primary intervention, hospital days, follow-up treatment and visits) compared with coronary artery bypass grafting (16,400 Euros per patient versus 18,800 Euros per patient; p<0.01).

Authors' conclusions
Spinal cord stimulation appeared to be an effective and safe treatment option in the management of refractory angina patients and of similar efficacy and safety to percutaneous myocardial laser revascularisation.
CRD commentary
The review addressed a clear research question and was supported by adequate inclusion criteria. A number of sources were searched. There was no language restriction, which reduced the risk of language bias. The review process was carried out with sufficient attempts to minimise reviewer error and bias.

The assessment of trial validity was performed well, and the authors reported on both individual quality items and a modified Jadad score. Adequate details of the primary trials were provided. The pooling of a trial where patients had no spinal cord stimulation implanted together with trials in which patients received an inactive spinal cord stimulation implantation may not have been appropriate. It was also unclear whether the authors pooled difference in change from baseline or at follow-up. The presence of statistically significant heterogeneity for some outcomes was not commented on or explored.

Given that the authors found either no statistically significant difference between the intervention and inactive comparator, or a statistically significant moderate effect size, the authors’ conclusions overstate the evidence presented.

Two authors disclosed financial links as consultants with Medtronic UK (manufacturers of spinal cord neurostimulators and funders of the review).

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that additional high quality RCTs in appropriately selected patients are needed. Any future trials should carefully consider the choice of comparator therapies, and should examine the question of value for money and comprehensively assess healthcare resource utilisation costs, and collect generic preference-based quality of life data (such as the European Quality of life questionnaire - EQ-5D).

Funding
Medtronic UK (manufacturers of spinal cord neurostimulators).

Bibliographic details

PubMedID
19320999

DOI
10.1186/1471-2261-9-13

Original Paper URL
http://www.biomedcentral.com/1471-2261/9/13/abstract/

Other URL
http://ukpmc.ac.uk/abstract/MED/19320999

Indexing Status
Subject indexing assigned by NLM

MeSH
Angina Pectoris /complications /physiopathology /therapy; Combined Modality Therapy; Complementary Therapies; Coronary Artery Bypass; Coronary Artery Disease /complications /physiopathology /therapy; Cost-Benefit Analysis; Databases, Bibliographic; Electric Stimulation Therapy; Exercise Tolerance; Humans; Male; Quality of Life; Randomized Controlled Trials as Topic; Spinal Cord /physiology; Treatment Outcome
AccessionNumber
12009110291

Date bibliographic record published
14/04/2010

Date abstract record published
16/02/2011

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.