Efficacy of Spinal Cord Stimulation in patients with Refractory Angina Pectoris; a randomized controlled trial

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Ethical review	Approved WMO
Status	Completed
Health condition type	Coronary artery disorders
Study type	Interventional

Summary

ID

NL-OMON55130

Source
ToetsingOnline

Brief title
SCRAP trial

Condition

- Coronary artery disorders

Synonym
refractory angina pectoris. End stage coronary artery disease

Research involving
Human

Sponsors and support

Primary sponsor: Catharina-ziekenhuis
Source(s) of monetary or material Support: ZonMW;project TopZorg

Intervention

Keyword: Neuostimulation, Refractory angina pectoris

Outcome measures

Primary outcome

Percentage of myocardial ischaemia (% of left ventricular myocardium) measured using PET perfusion scan after six months and after twelve months treatment with spinal cord stimulation, compared to baseline.

Secondary outcome

Effect of spinal cord stimulation treatment in patients with refractory angina pectoris on:

- Changes in absolute quantification of myocardial blood flow using PET perfusion scan including myocardial blood flow (MBF) & myocardial flow reserve (MFR) regionally and globally.
- Patient condition using the 6-minute walking test
- Frequency of angina pectoris attacks using the Seattle Angina Questionnaire
- Severity of angina pectoris attacks using the Numeric Rating Scale (NRS) score
- Grading of angina pectoris using Canadian Cardiovascular Society (CSS) class
- Quality of life using the RAND-36 Questionnaire
- Frequency of short-acting nitroglycerin use using the Seattle Angina Questionnaire
- Major Adverse Cardiac Events (MACE): - Number of hospital admissions due to acute coronary syndrome (ACS); - Revascularization (CABG and/or PCI); - Number of presentations at the emergency room (ER) due to angina pectoris; - Cardiovascular mortality

- Safety endpoints: Number of device infections (lead and/or battery; - Number

of device dislocations (lead and/or battery); - Number of lead fractures.

Evaluation at six and twelve months after study inclusion.

Study description

Background summary

In recent decades, evolution of medical therapy, coronary artery bypass grafting (CABG) and percutaneous coronary interventions (PCI) significantly reduced the morbidity and mortality in patients presenting with stable coronary artery disease (CAD). Despite all treatment innovations, 5 - 10% of patients with stable CAD remain symptomatic with optimal therapy referred to as *refractory angina pectoris (RAP)*. This condition is defined as a *chronic condition (> three months) characterized by diffuse coronary artery disease in the presence of proven ischemia, which is not amendable to a combination of medical therapy, angioplasty or coronary bypass surgery*. Patients with RAP are severely restricted in performing daily activities due to debilitating angina complaints, leading to decreased quality of life.
Spinal Cord Stimulation (SCS) is one of the treatment options for patients with RAP. SCS is a device with a lead located in the epidural space that provides neurostimulation. Transcutaneous Electrical Nerve Stimulation (TENS) has the same effect as SCS but is used by applying two adhesive electrodes to the skin (in the thoracic region) to provide neurostimulation. Four possible mechanisms explaining the beneficial effects of SCS/TENS on RAP have been described; reduction of pain perception, decreased sympathetic tone, reduced myocardial oxygen demand, and improved coronary microcirculatory blood flow.
Research into the effect of SCS on RAP has mainly been observational studies. Only four placebo-controlled randomized controlled trials have been performed up to date comparing different settings of neurostimulation (normal, subthreshold and sham), with differing results (3-6). Reduction of angina pectoris attacks due to SCS was proven in all studies. But it is not clear if there is a placebo effect as suggested by the study of Zipes et al. This study showed no significant differences between the high and low stimulation groups whereas the other two studies did show differences between the groups at different levels of stimulation. The inclusion of patients was slow in these studies, were underpowered and one study had to be terminated early, making the interpretation of the results all the more difficult. The primary end point of these studies was also based on frequency of angina pectoris, a soft endpoint.
The recently published ESC guideline *chronic coronary syndromes* mention

non-existing to promising levels of evidence with regard to treatment options in patients with RAP and concludes that SCS may be considered (Class IIB; level of evidence B). It concludes that, *Larger RCTs are required to define the role of each treatment modality for specific subgroups, to decrease non-responder rates and ascertain benefit beyond potential placebo effects*

Study objective

The aim of this study is to determine whether treatment with spinal cord stimulation in patients with refractory angina pectoris leads to a significant reduction in myocardial ischemia. Other aims are to determine the effect of this treatment on the frequency of angina pectoris attacks, the effect on quality of life, use of short-acting nitrates, patient condition using the 6-minute walking test, clincical outcomes (hospitalizations, percutaneous interventions, coronary artery bypass grafting), as well as possible complications arsing from the spinal cord stimulator implantation (secondary outcome measures).

Study design

It is a double-blind, cross-over, placebo-controlled, single centre randomized controlled trail.

Intervention

All patients who participate in this study will receive an implanted spinal cord stimulator. The spinal cord stimulator that will be implanted consists of one battery, one lead and a remote control. With the remote control the patient can change the desired level of stimulation. The lead will be placed in the epidural space at the cervico-thoracic level.

After implantation of the spinal cord stimulator an installation programmer will be used by the dedicated pain nurse to input the mode of stimulation. When the installation programmer is used the spinal cord stimulator will be programmed to think that two leads are connected to the battery whilst only one lead has been implanted and connected to the battery. When programming the spinal cord stimulator it will be possible to a) stimulate the actual lead located in the epidural space, b) stimulate the non-existent second lead. What this means is that the patient can use the remote control to change the level of stimulation in both situations, whilst no stimulation occurs if the non-existent second lead has been programmed to stimulate.

The patient will be informed that during the study he will receive six months of high-density neurostimulation, i.e. actual lead, and six months of no neurostimulation. The high-density form of stimulation does not usually lead to parasthesia. During the entire study period (both in the six months the SCS is

on and in the 6 months the SCS is off) the patient will be able to use the remote control.

This study design is deemed safe because in this patient population there are no more treatment options available and spinal cord stimulation is an *additional* last resort* treatment option. All patients participating in this study will receive optimized standard care which is the same as the treatment all patients with refractory angina pectoris in the Netherlands receive.

For the randomisation procedure the online program Research Manager will be used. After the spinal cord stimulator has been implanted randomisation will take place into Group A starting with *Stimulation On - High-density* or Group B starting with *Stimulation Off - No stimulation*;
- Stimulation On - High-density: The lead in the epidural space will be stimulated using high-density stimulation and is referred to as *high-density mode*. During this period the patient will not feel paraesthesia*s in the thoracic region. This is the effective treatment option.
- Stimulation Off - No stimulation: The programmed second non-existent lead will be programmed as active, whilst leading to no neurostimulation and is referred to as *no stimulation*. Tthe patient will not feel paraesthesia*s during this period but he will be able to change the level of stimulation. This is the placebo treatment option. The lead in the epidural space will not be used during this period.

After 6 months cross-over will take place, meaning that Group A is switched to 'Stimulation Off - No stimulation' and Group B is switched to 'Stimulation on - High-density'. When the study has finished (after 12 months), the spinal cord stimulator will be changed in all patients to the conventional stimulation mode.

Study burden and risks

During this study the patient will have to come to the hospital a total of 7 times. The first visit is for screening purposes to determine whether the patient can participate in the study (by performing the TENS-test using a treadmill). If the patient is eligable, first a PET-scan will be performed (rest and stress) to determine whether myocardial ischaemia is present (this PET-scan is part of the regular care). If myocardial ischaemia is present, then the patient is eligible to participate in the study.Two visits to the out-patient clinic will be done to explain the study to the patient, answer questions and, if the patient wants to participate, written informed consent. At this time a six-minute walking test will be performed. Next the patient will come to hospital for the duration of 1 day and night for the implantation of the spinal cord stimulator and will receive intraveneous antibiotics for prevention of an infection of the device and/or the surgical wounds.
After the implantation the patient will be seen at the outpatient clinic at 1, 3, 6 and 12 months. Prior to the 6 and 12 month visits the patients will be

asked to fill out two questionnaires at home (taking a maximum of 30 minutes) and take these with them to the outpatient appointments. During the outpatient visit at 6 and 12 months the 6-minute walking test will be repeated.
After the implantation the PET-scan will also repeated (stress only) at 6 and 12 months, this will take approximately 60 minutes and the patient will receive instructions prior to the scan in preperation. Over a period of 12 months, the patient will undergo 3 PET-scans, and the radiation exposure has been kept to a minimum.
The overall burden and risks (mainly possible complications arising from the implanted spinal cord stimulator) of this study are acceptable. These patients have been diagnosed with refractory angina pectoris for which we know are no further treatment options. From the literature we know treatment with spinal cord stimulation leads to a reduction in the number of angina pectoris episodes and an improved quality of life. This is why we conclude that the possible benefits in this patient group outweigh the possible risks and burden associated with this study.

With regard to the spinal cord stimulator; the device will remain in situ after the study has been finished. The device will be set to conventional stimulation.If the patient wants the device removed, this can be discussed with the researchers and the spinal cord stimulator can be explanted. If an infection of the spinal cord stimulator should occur, then (part of) the spinal cord stimulator will have to be removed. it will be possible to place a new spinal cord stimulator at a later date.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Refractory Angina Pectoris: - Stable angina pectoris CCS class III or IV, with a minimum of 5 episodes of angina pectoris over the course of one week, during a minimum period of three months prior to screening; - Coronary angiogram (CAG) performed within the last 12 months showing significant coronary artery disease defined as at least one coronary artery stenosis of >75% or 50 - 75% with proven ischaemia (see below), not suitable for revascularisation. Confirmed by one (or two in case of doubt) interventional cardiologist based on CAG images; - Optimal anti-anginal medication. Patients should at least use; b-blocker and/or calcium channel blocker, short- and/or long-acting nitrate. If the patient doesn*t use one of these groups of medication the reason (side-effects) should be clear.
- Proven ischemia: - MIBI-SPECT: summed stress score (SSS) of at least 1, in combination with summed difference score (SDS) of at least 1 (1-4 mild ischaemia, > 4 moderate to severe ischaemia); - FFR: < 0.80, with no intervention options (determined by intervention cardiologist); - MRI perfusion: >= 1 segment of subendocardial hypoperfusion during stress perfusion, not present at rest and no matching fibrosis (using 16 segment AHA heart model); - PET: Semi-quantitative measurement: SSS score of at least 1, in combination with SDS score of at least 1 (1-4 mild ischaemia, > 4 moderate to severe ischaemia). Quantitative measurement: reduced myocardial perfusion reserve.
- No revascularisation (PCI and/or CABG) performed between ischaemia testing and study inclusion.
- Age 18 years or older

Exclusion criteria

- Acute coronary syndrome (ACS) during three month period prior to screening
- Life expectancy less than 12 months
- Inability to perform a 6-minute walking test
- Inability to give informed consent

- No proven ischemia (see Inclusion criteria for definition)
- Spinal cord disease which could prevent correct positioning of the lead in the epidural space; to be determined by the anaesthesiologist performing the implantation
- Anticoagulation therapy that cannot be stopped prior to spinal cord stimulator implantation
- Inadequate paresthesia coverage, during implantation, of the thoracic region where angina complaints are localized
- Pregnancy
- Mild Cognitive Impairment or dementia
- Concomitant symptomatic valvular heart disease including severe aortic stenosis and/or regurgitation, severe mitral valve stenosis and/or regurgitation or severe tricuspid valve regurgitation.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	14-12-2021
Enrollment:	72
Type:	Actual

Medical products/devices used

Generic name:	Spinal Cord Stimulator (PrimeADVANCED SureScan® myStim)
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	15-04-2021
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-08-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-12-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL75114.100.20