State-of-the-art nuclear neuroimaging in failed back surgery syndrome: can we predict the outcome?

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Primary Objective: The primary objective of this study is to map cerebral glucose metabolism of patients diagnosed with FBSS in an effort to elucidate imaging biomarkers that could predict the effectiveness of SCS treatment. Secondary Objectives:...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Spinal cord and nerve root disorders
Study type	Observational non invasive

Summary

ID

NL-OMON51773

Source
ToetsingOnline

Brief title
FDG PET brain in FBSS prior to SCS

Condition

- Spinal cord and nerve root disorders

Synonym
Post-laminectomy syndrome; persistent lower back and/or leg pain after spinal surgery

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: FBSS, Nuclear neuroimaging, Outcome prediction

Outcome measures

Primary outcome

The main study parameter is metabolic glucose activity of cerebral regions associated with pain. This will be measured by F18-FDG PET-CT scans, which provide information on the (semi-)quantitative uptake of the F18-FDG radiotracer in the brain. This radiotracer is a positron emitting molecule and its chemical structure is very similar to glucose. Thus it acts like an analogue, mimicking distribution patterns of glucose and accumulating in tissues with elevated glucose demand (32). The F18-FDG PET-CT scans will be performed prior to SCS implantation of FBSS patients. Data of FBSS patients will be compared to a readily available database of healthy individuals.

Secondary outcome

The secondary parameter of this study is SCS outcome. This will be determined by questionnaires which explore pain experience, interference of pain with daily life and overall quality of life prior to SCS implantation and at set follow-up moments of 1, 3 and 6 months post SCS implantation. The Dutch version of the brief pain inventory (BPI) will be used to explore pain experience and interference of pain with daily life. Quality of life will be assessed by use of the EQ5D. These questionnaires are provided in file F1. Additionally, potential complications of SCS will be monitored.

Baseline characteristics and patient specific history of all patients will be

examined to ensure a complete overview of the studied population can be provided. Baseline characteristics of patients will include gender, age, height, weight and BMI. These baseline characteristics are also necessary for adequate PET-CT imaging and dose administration. Patient specific history will include information on comorbidities, FBSS treatment and history (e.g., years suffered from FBSS, the type and amount of spinal surgeries, treatments, therapies and an extensive assessment of pain medication). Comorbidities that could interfere with PET-CT validity will be established prior to inclusion and will prevent patients from participating in the study.

Study description

Background summary

Nowadays chronic back pain is a health concern that effects people of all ages world-wide. It is recognized as one of the main contributors to the number of disability-adjusted life years (DALYs) globally (1). Most cases of chronic back pain are caused by failed back surgery syndrome (FBSS) (2). This is a condition where one or more spinal surgeries fail to relieve lower back pain with or without pain radiating to the lower limbs. Previous studies report 10-40% of people who have undergone spinal surgery continue to suffer from their pain symptoms post-surgery (3). The majority of surgeries were technically carried out correctly but did not result in improvement of pain symptoms. Studies investigating the aetiologies of pain persistence provide incongruent reports. Some studies found that 90-95% of FBSS cases are not caused by surgery, and that some intrinsic factor must be at play. While other studies have found the opposite to be true, suggesting 90% of FBSS cases are caused by surgeries. One of the explanations for this high percentage being misdiagnosis before surgery (4).

For some patients anatomical abnormalities result in their pain symptoms, but for others the exact cause is not that clear. For these patients imaging techniques such as MRI scans are unable to detect any anatomical abnormalities, which implies functional impairment (5). An example being impairment of the sympathetic nervous system (SNS), which has been documented in FBSS patients before (6, 7).

Therapy options after surgery are often aimed at the most probable cause of pain. Treatment options for FBSS include pharmacological interventions, physical therapy, exercise, behavioural rehabilitation, neuromodulation and even re-surgery (8). Remarkably, the chance of clinical improvement is reduced exponentially with each subsequent surgery (9). In recent years neuromodulation has been recognized as an effective long-term treatment option for FBSS (8, 10). As a result, neuromodulation treatment has started to become more customary. (11). Spinal cord stimulation (SCS) being one of the neuromodulation treatment options. However, SCS treatment is not without its risks and complications and is thus seen as a last resort treatment option. One of the most critical risk being infection potentially resulting in meningitis. Other complications include migraines, reported by 12% of SCS cases, and pain at the site of implantation, which is reported by 9% of SCS cases (12). Besides these complications the effectivity of SCS treatment also varies greatly from person to person, ranging from no pain reduction at all to a reduction of 88% (12, 13). The costs of SCS treatment are not negligible either, the per-patient-average in the USA is currently $48,357 (14). The investigation of predictive biomarkers that could foretell the effectiveness of neuromodulation before treatment could help reduce these unnecessary health and financial burdens on patients suffering from FBSS.

To date, no studies have been performed on potential imaging biomarkers that could predict the effectiveness of SCS treatment. However, a recent study has shed light on imaging biomarkers in a different neuromodulation treatment option of chronic low back pain. This study investigated patients with low back pain who received L2-dorsal root ganglion stimulation as treatment. Prior to the intervention, patients underwent Positron Emission Tomography (PET) imaging of the brain with the radioactive radiotracer F18-fluorodeoxyglucose (F18-FDG) to asses cerebral metabolic activity. The study reported increased metabolic activity in the cerebral areas associated with nociceptive brain matrices (15). Other studies have also observed metabolic changes in area such as the thalamus, anterior cingulate cortex and primary and secondary somatic areas. Changes in these areas could influence cognition, attention, emotions and perception of pain (16-18). The use of F18-FDG PET-CT scans could further the understanding of disturbed metabolic glucose activity which could aid in the search for imaging biomarkers to help predict SCS effectiveness in patients suffering from chronic back pain.

Therefore, this study aims to map metabolic cerebral activity of patients suffering from FBSS with F18-FDG PET-CT scans to elucidate biomarkers that could help predict SCS effectiveness. This study also aims to deepen current knowledge on dysregulation in the brain of FBSS patients.

Study objective

Primary Objective: The primary objective of this study is to map cerebral glucose metabolism of patients diagnosed with FBSS in an effort to elucidate

imaging biomarkers that could predict the effectiveness of SCS treatment.

Secondary Objectives: Secondary objectives of this study are to establish a better understanding of the pain neuromatrix. Moreover, to better understand the pathophysiological mechanisms that result in FBSS, by mapping cerebral glucose metabolism of people who suffer from FBSS and comparing them to an already existing database of healthy subjects.

Study design

The design of this study regards a single-arm prospective observational study. The intention is to include 20 patients who suffer from FBSS and are scheduled to receive neuromodulation treatment in the form of SCS. Data collected from these patients will be compared to available data from healthy individuals.

Patients will be informed about this study and its objectives by a nurse practitioner/pain physician during regular consultations prior to implantation of an SCS system. Patients who meet all criteria and are willing to participate will be informed about this study and will receive a patient information letter (file E1) after which they will have a reflection period. Patients will have the possibility to consult an independent physician who is informed about the protocol but not actively involved in this study. After one to two weeks, patients will be telephoned to answer remaining questions. If they are willing to participate, they will sign a written informed consent (file E2). Thereafter, additional questionnaires which will chart their pain intensity, pain characteristics, interference of pain with daily life and overall quality will be provided and filled in prior to PET-CT imaging and the SCS treatment. The additional questionnaires are provided in file F1.

Patients who are willing to participate in this study will be referred to the Dutch hospital where PET-CT neuroimaging will take place (Radboudumc, Department of Nuclear Medicine). The images will be taken by employees of Radboudumc Nijmegen; Department of Anaesthesiology, Pain and Palliative Medicine.
Patients will be invited to undergo PET-CT imaging of the brain at least two weeks prior to receiving SCS implantation surgery. PET-CT imaging of the brain will not delay the clinical progress of the patient to receive SCS.

The surgical procedure for SCS consists of two phases: a trial phase and an implant phase, both are performed under sedated analgesia and protocollary antibiotics. This surgical procedure is safe and has a low rate of complications (19, 20). SCS is a standard therapy covered by basic health insurance in the Netherlands. This study is without additional risks. Therefore, we request a dispensation from the statutory obligation to provide insurance.

After the SCS system is implanted, the patients will be asked to fill in the

same questionnaires they filled in at baseline. These will be filled in after 1 month, 3 months and 6 months post-implantation. If the SCS system needs to be removed during this time period (e.g. due to infection), the patient will be excluded from this study. The duration of the study is six months for each patient after they have undergone PET-CT neuroimaging.

Study burden and risks

Patients participating in this study will undergo a F18-FDG PET-CT scan of the head. The main risk involved with this imaging technique is radiation exposure, this exposure to radiation adds to the lifetime radiation of participants and might increase the risk of cancer. To decrease this risk patients will be exposed to the lowest level of radiation achievable for adequate imaging results. The radiation dose will be approximately 4 mSv, which is considered to be minimal to low.

This form of medical imaging is the only way to investigate the study objectives. Answering these objectives could lead to a better understanding of FBSS, the pain neuromatrix and predictive biomarkers for SCS outcome. As the pathophysiology of FBSS is not understood and predictive biomarkers have never been identified. Failed back surgery syndrome is already a substantial health concern and the incidence and prevalence is expected to increase as the global population is aging (1, 22). A recent study has already shed some light on the neurology of low back pain. This study explored the cerebral glucose metabolism of patients with discogenic low back pain who received L2 DRG stimulation with F18-FDG PET-CT scans (15).

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

• Aged between 18 and 75 years
• Diagnosed with FBSS with low back pain radiating in lumbar segments L4, L5 and S1 with or without pain in the lower limbs
• Experienced chronic pain for >= six months with a pain score >= 5 for the weighted Visual Analogue Scale (VAS)
• No option for further surgical intervention
• Previous pain treatments have been unsuccessful (insufficient pain relief or unacceptable side effects)
• Psychologically screened
• Willing to provide informed consent
• Scheduled to receive neurostimulation treatment (i.e., SCS)

Exclusion criteria

participation in this study:
• Younger than 18 years old
• Presence of clinically significant (e.g., Alzheimer*s disease, frontotemporal dementia, Parkinson*s disease) or disabling chronic pain condition as this will limit the validity of PET-CT imaging and the outcome of SCS treatment. To test for neurodegenerative disorders, well-validated, Dutch versions of the mini-mental state examination (MMSE) and the frontal assessment battery (FAB) tests will be used
• Patients with diabetes mellitus (either type I or type II)
• The expected inability of the patients to properly operate the neurostimulation system
• A previous SCS procedure
• Addiction to drugs, alcohol (>= 5 E / day) or medication

• Insufficient cooperation (lack of motivation, understanding)
• History of coagulation disorders, lupus erythematosus, diabetes mellitus, rheumatoid arthritis or Morbus Bechterew
• Current use of medication affecting coagulation which cannot be temporarily stopped
• Medication usage that could interfere with biodistribution of F18-FDG tracer (e.g., benzodiazepines, barbiturates)
• An inability to speak or understand the Dutch language
• Life expectancy < 1 year
• Patients with a pacemaker
• Local infection or other skin problems in the operation area
• Existing or planned pregnancy

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	20-01-2023
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO Date:	06-07-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-03-2023

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-10-2024
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	NL79907.091.22