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Deep brain stimulation for chronic post-stroke pain

Submission date
09/12/2019

Recruitment status
Suspended

Registration date
17/12/2019

Overall study status
Stopped

Last Edited
09/06/2021

Condition category
Signs and Symptoms

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Chronic pain is common with moderate to severe disabling pain affecting between 10.4 to 14.3% of the UK population. It is frequently associated with damage to nerves or the brain, this is called neuropathic pain. Chronic neuropathic pain can occur after strokes in up to 20% of stroke patients (Central Post Stroke Pain, CPSP) and this form of pain can be difficult to treat with standard medical therapies. Deep brain stimulation (DBS) surgery involves the insertion into the brain of electrical leads connected to a pacemaker device similar to that used in the heart. This allows regions of the brain to be stimulated, allowing controlled alterations in function of brain networks. Brain regions associated with pain perception have been described, together known as the central pain network, and alterations to this network have been proposed to underlie CPSP. DBS is an intervention that allows clinicians to intervene in the functions of this network with the aim of improving pain symptoms. However, DBS is a surgical procedure with risks and a financial cost. The aim of this study is to find out whether this form of intervention is safe and effective at treating pain in stroke patients.

Who can participate?
Patients aged 18 and over with central pain after a stroke who have had the pain for at least 2 years, which has not been controlled with medicines or other measures.

What does the study involve?
The researchers follow the participants for 14 months after the surgery to assess their response to the surgery. This involves telephone and face to face consultations where they ask a series of questions about pain and disabilities. They switch the stimulation off for a period of the study after surgery, unbeknown to the person asking the questions, to try to gauge if the stimulation is effective or not.

What are the possible benefits and risks of participating?
The potential benefit is good pain control. The main risks of neurosurgery are infection, scarring and more seriously symptoms similar to stroke such as worsened weakness, sensation change or symptoms affecting speech or vision (not an exhaustive list). In the worst case scenario there is a small risk of death from surgery or further emergency surgery.

Where is the study run from?
Oxford University Hospitals NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
January 2020 to July 2023

Who is funding the study?
The Jon Moulton Charity Trust (Guernsey)

Who is the main contact?
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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
264275

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
CPMS 43544, IRAS 264275

Study information

Scientific Title
A pragmatic assessor-blinded randomised controlled trial of deep brain stimulation for chronic post-stroke pain

Study objectives
Chronic pain is common with moderate to severe disabling pain affecting between 10.4 to 14.3% of the UK population. It is frequently associated with damage to nerves or the brain, this is called neuropathic pain. Chronic neuropathic pain can occur after strokes in up to 20% of stroke survivors (Central Post Stroke Pain, CPSP) and this form of pain can be difficult to treat with standard medical therapies. Deep brain stimulation (DBS) surgery involves the insertion into the brain of electrical leads connected to a pacemaker device similar to that used in the heart. This allows regions of the brain to be electrically stimulated, allowing controlled changes in the function of brain networks. Brain regions associated with pain perception have been described, together known as the central pain network, and alterations to this network have been proposed to underlie CPSP. DBS is an intervention that allows clinicians to intervene in the functions of this network with the aim of improving pain symptoms. However, DBS is a surgical procedure with risks and a financial cost. Moreover, there is no randomised controlled trial evidence, the gold standard of medical evidence, that the intervention works. The researchers propose to undertake such a trial to study if this form of intervention is effective at treating pain in stroke patients.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 31/01/2020, South Central - Oxford A REC (Level 3, Block B, Whitefriars, Lewins Mead, Bristol, BS1 2NT, UK; +44 (0)207 104 8041; oxforda.rec@hra.nhs.uk), ref: 19/SC/0559

Study design
Randomised; Interventional; Design type: Treatment, Device, Surgery

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Chronic post-stroke pain

Interventions
The design is a pragmatic assessor-blinded, randomised controlled trial. The design seeks to exploit the feature of deep brain stimulation technique that the surgery to implant the DBS device is not the treatment effect, rather the electrical stimulation of the targeted region is.

The trial team will be divided into clinical members and research members. The participant themselves and the nurse specialist will not be blinded, but surgical members of the clinical team and the researcher (assessor) who performs participant assessments will be blinded as to whether the stimulation is on or off in the participant at all point postoperatively. Participants will be counselled as to avoid giving clues to the researcher as to whether stimulation is on or off through an augmented consent process.

To identify a placebo effect of the surgery itself before the randomisation phase, participants will undergo a 2-month period off stimulation after surgical implant of the DBS device. Researcher (assessor) will be blinded as to whether the individual participant is on or off stimulation at all phases post-surgery.

Trial design
The DBS for CPSP trial is an assessor-blinded single centre randomised controlled trial comparing DBS stimulation with absence of stimulation in individual participants. The trial has two prospective cohort arms, pre-randomisation to assess for placebo effects from the surgery itself and post-randomisation to assess the effect of any changes in stimulation parameters.

The elements of the trial are:
Clear distinction between research and clinical roles
Screening
Recruitment
Surgery
Cohort OFF stimulation
Randomisation
Cross over
Prospective cohort ON stimulation

Separation of research and clinical roles:
The researchers define four roles in the trial. Each role may be performed by more than one person, but each person may only have one role. The research and clinical roles are non-overlapping and each is blind to the information held by the other until the analysis stage. The roles are:
• Surgeons perform surgery, and are blind to research results until trial analysis
• Assessor (Researchers) to do questionnaires of the research test battery (e.g. VAS, MPQ, etc.), they book radiological scans for research, but are blind to stimulation ON or OFF (except pre-operatively) and surgical details until trial analysis

• Nurse specialist (NS) to do programming, they are not blind to stimulation status, and do randomisation phase clinical follow up. They keep their own notes which are not part of research assessments, although randomisation details and medication usage disclosed at the trial analysis phase. They are always available as first contact for any issues related to the surgery post-operatively including device management.
• A data analyst who analyses the trial data generated by the assessor and details recorded by the nurse specialist.
The analyst is not involved in the clinical follow up of the participants and does not collect research data during the trial.

Recruitment
Patients will be recruited using an augmented consent procedure, from those interested patients that prima facie appear suitable for the trial interventions and are willing to consider these. Potential participants are identified by specialist doctors who include GPs, pain team consultants and stroke physicians, who we ask to write a medical letter on the potential participants' behalf with specific reference to the main inclusion criterion: chronic post-stroke pain, >2 yrs duration, refractory to at least 1 opiate, 1 antiepileptic drug, 1 antidepressant and mean VAS score >7/10 despite MDT input. We ask the specialists to give this letter to the potential participant to give to the study team once the participant has consented for research. These specialists will have been provided with information and publicity material approved by the ethics committee in advance. They will also have been provided with electronic copies of the participant information sheet for themselves and potential participants. The potential participant is given a patient information sheet and contact details for the trial, including the proviso that the participant must make first contact with the trial team before any further arrangements are made. The specialist's letter is not available to the team until the participant has consented for research (see below).
The aim of the recruitment phase is ultimately to gain the consent of the participant as they will be an active member of the research. The researchers want them to fully understand what the surgery is, the risks, the potential benefits, the reason why they want to do a trial and why it is important to assess the effects of the stimulation ON and OFF over the next year after the surgery. To achieve this the researchers propose an augmented consent process (Maslen, et al., 2018). The augmentation is to have three meetings by different members of the team rather than one meeting, all as an outpatient.

This involves:
• Appointment with Assessor to provide information of the level of participation required for the research arm: pre and post-operative test battery of questionnaires, timing frequency, level of involvement, pre-op fMRI, trial design including blinding of the assessor and randomisation, and cohort prospective phase. The purpose of randomisation will be discussed, i.e.(see below), what this involves, what happens after randomisation period, and why assessor will not ask or know about clinical matters, (this will be the role of the nurse specialist). The assessor underlines that participation is voluntary and participants may opt-out at any point but this may mean the DBS device should be removed.
• Appointment with Surgeon. Surgery is only offered on the basis that the research follow up is an integral part of the surgical intervention. The surgeon describes the procedure, esp especially that some of this is awake, and the risks, including to life. The hoped-for benefit of surgery is discussed (good pain relief) but that this is not guaranteed therefore our need for a trial to know if it is worthwhile. The post-operative OFF period is discussed. The participant is told the surgeon will see patient the participant in this OFF period to check for complications but not in the randomisation period except if asked by nurse specialist. The surgeon but will see the participants again after the end of randomisation phase. If the participant is on anticoagulants, the necessity to stop these for a period before and after surgery is discussed, including the risk

of a short period off anticoagulants. If the risk is unacceptable to stop anticoagulants for a short period, this is documented and the potential participant is excluded from the trial.
• Appointment with Nurse specialist. They are the unblinded first responder to the patient after surgery. They will also explain the OFF period after surgery, then inform the participant that they will be randomised to ON or OFF after this period. The Nurse specialist will see patient in this phase whether ON or OFF. Assessor will assess the effect of surgery in this phase but it will be stressed that the assessor is not clinical, so will not ask about the surgery, this will be nurse's job and the participant will be asked not to communicate any details except to answer the assessor's direct questions. Nurse specialist will keep their own notes, but these are not shared with assessor or data analyst except during analysis of the trial results. They will be shared with the surgeon if needs be.
• These appointments can be same day and same location but separate personnel, not together. This is because stroke patients may be poorly mobile therefore multiple appointments may be difficult
• The researchers will send a single letter with details of all discussed edited by assessor, nurse and surgeon.

If the participant agrees to take part, informing the nurse specialist of their decision after the first meeting by telephone or email, the first stage of research is arranged. Potential participants will be contacted by telephone 1-2 weeks after the initial meeting if they have not contacted the team before this. The first stage in research involves signing the study informed consent form (by the assessor), giving the specialist's letter to the study team after consenting to this, neuropsychological assessment, functional MRI tests and test battery assessment by the assessor. It is made clear to the participant that the medical information provided by the participant's specialist, neuropsychological assessment, MRI or test battery may disqualify the participant for surgery. Potential participants undergo screening for eligibility assessment for surgery after this first stage and having given consent to the study team being able to access medical information contained in the participant's specialist's letter. This will take place in the neurosurgical offices of the John Radcliffe Hospital by the clinical members of the team. The source data of the screening procedure will be letters from specialists (e.g. Pain Management Centre, Churchill Hospital, GPs) or medical physicians, and preliminary research information. This is to assess if individuals meet the inclusion criteria described above, and the absence of exclusion criteria. In the absence of contraindications, after the tests are complete, the participant is listed for surgery, being informed of the outcome of the tests by the study team. Participants who do not meet the inclusion criteria/who meet the exclusion criteria will be informed at this stage and will not continue in the trial.

The test battery - questionnaires:
• Pain severity: Visual analogue scale (VAS), McGill Pain Questionnaire (MPQ), brief pain inventory (BPI))
• Assessment of affective component of pain: Montgomery Asberg Depression Rating Scale (MADRS), McGill Affective Pain index
• Neuropsychological outcomes: Wisconsin Card Sorting Test, Weschler Memory Scale III, Intra-/Extra-Dimensional Set-Shifting, Spatial Span, Spatial Working Memory, Verbal Fluency, Repeatable Episodic Memory Test, Story Recall Test (from the adult memory and information processing battery) and Raven's Standard Progressive Matrices
• Quality of life: EQ5D = EuroQol-5D (EQ-5D), Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36), Hospital Anxiety and Depression Scale (HADS) and the Functional Limitation Profile (FLP)

Admission for surgery
• The surgeon confirms the participant wishes to take part in research, specifically

randomisation, surgery and follow up. Participant signs and surgeon checks the informed consent form for research. If the participant declines, they do not proceed to surgery – surgery is only offered on a trial basis
• A separate consent form for surgery is completed as per hospital protocol.

Surgical procedure – 0 months
• Stage 1 and 2 surgery. The surgery takes place in two stages on the same day (Owen et al., 2006). An MRI is required pre-operatively as an outpatient, which can be simultaneous with fMRI:

Stage 1 surgery
This involves implantation of the DBS lead into the target nuclei in the brain, namely the sensory thalamus and periaqueductal grey matter. This involves placing a CRW frame on a participant's head with fiducials, then performing a CT head scan and fusing this to the MRI scan to plan the operation. The participant is prepared for surgery (awake with local anaesthetic) and undergoes the insertion procedure.
Test stimulation during awake surgery will be carried out to assess electrode placement. The aim is to achieve somatotopic coverage (indicated by paraesthesia experienced by the participant) in the painful area. After implantation (and adjustment if necessary) the participant is transferred to the radiology department for a CT head to check lead position and for any bleeding caused by the surgery radiologically.

Stage 2 surgery
Full implantation of the leads and implantable pulse generator will be performed under general anaesthesia during the same surgical session in theatre. A subcutaneous pocket will be created for the implantable pulse generator (IPG) (typically placed subcutaneously in the pectoral region or anterior abdominal wall) and extension leads will be passed under the skin pocket up to the scalp, and connected to the IPG below and depth leads above. Finally, the IPG will be interrogated telemetrically to ensure that the system is functioning correctly.

Post-surgery – 0 - 2 months
• All patients have stimulation OFF at least for 2 months, no exceptions. This is to allow healing of the surgical target and allow any ‘stun effect’ from the surgical procedure to wear off. The participant will continue medications as prescribed by their pain physician that in many cases will be their GP. Medication usage will be documented by the nurse specialist during the trial, only disclosed at the analysis stage to other members of the team. The medications will not be managed by the study team, the participant may use whatever medications are prescribed by their usual pain physician.
• The test battery is performed by assessor in this OFF period, to provide baseline postsurgical data. This is performed in clinic after the surgeon and nurse specialist have seen the patient to assess for complications on the same day and location. The results of the battery are not shared with the patients or clinical team.
• Complications such as infection may require further surgery in which case the participant will not continue in the trial and in most cases involve surgery to remove the DBS device or replacement of components of the device. This will be treated as an AE/SAE and treated accordingly.

Randomisation – 2 - 5 months
• After the OFF period, participants are randomised to ON or OFF stimulation by computer, details are only known to nurse specialist, not surgeon or assessor at this stage. The pacemaker device is managed accordingly by the nurse specialist.
• ON and OFF patients are both seen by nurse specialist only in this period
• The ON stimulation participants are programmed in this phase, OFF stimulation participants

are simply assessed by nurse specialist
• Nurse specialist is available for follow up in randomisation period, but not surgeon primarily, although available if needed in the case of possible complications.

Research follow up over 3 months of first randomisation
• Telephonic follow up is performed by assessor, but have 1 appointment in person (dependent on patient mobility). The assessor is blind to ON or OFF status and surgical details. The nurse specialist will see or have telephonic contact with the participant first on these days. The assessor will not ask about surgical matters at this appointment, they will only ask questions for research. Participant will have been told this pre operatively and reminded by nurse specialist about this, being asked to only answer to assessor's questions and not offer any additional information.

Cross over – 5 – 8 months
• After 3 months, ON and OFF groups are crossed over – ON are switched OFF and vice versa by nurse specialist.
• Assessor follows up with monthly telephonic pain assessment test battery as for the randomisation stage, once in person. The participant is seen by or contacted by telephone by the nurse specialist the same day before assessor, who is blinded to stimulation status.

Prospective cohort open-label phase 8 months – 14 months
• At 8 months all participants have their DBS device switched ON, if the participant agrees.
• Participants are followed up by the nurse specialist as appropriate, with adjustments made to stimulation to gain the optimum treatment effect
• 11 months and 14 months, assessor follows up with test battery still blinded to the device status
• Surgical follow up with surgeon at end of blinded period (if not required before)

End of trial
• End of trial – last participant completes 1 year follow up after randomisation (month 14 postoperatively.

Intervention Type
Other

Phase
Phase III

Primary outcome(s)
Pain experience of participants assessed by the following tools by a member of the research team pre operatively and post operatively, blinded as to whether stimulation is on or off in the first 6 months post-operatively, then unblinded after 6 months:
1. Pain severity assessed using the Visual analogue scale (VAS), McGill Pain Questionnaire (MPQ), brief pain inventory (BPI))
2. Affective component of pain assessed using the Montgomery Asberg Depression Rating Scale (MADRS), McGill Affective Pain index
3. Quality of life assessed using EuroQol-5D (EQ-5D), Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36), Hospital Anxiety and Depression Scale (HADS) and the Functional Limitation Profile (FLP)
4. Neuropsychological test battery (Wisconsin Card Sorting Test, Weschler Memory Scale III, Intra-/Extra-Dimensional Set-Shifting, Spatial Span, Spatial Working Memory, Verbal Fluency,

Recall Test (from the adult memory and information processing battery) and Raven's Standard Progressive Matrices)

Key secondary outcome(s))
1. Pre-operative neuroimaging and pain assessments to develop algorithms which help predict response to test stimulation and thus improve patient selection. Specific measures are resting-state functional connectivity, task-related functional network connectivity and diffusion-weighted tensor imaging of connectivity of targeted regions i.e. the sensory thalamus or periaqueductal grey.
2. Economic impact of the surgical intervention, assessed using patient-level resource use data including health and social care costs relating to the intervention (e.g. surgical costs, drug costs, hospital stay, GP costs, referrals etc). In line with recent recommendations from the National Institute for Health and Clinical Excellence (NICE) the economic evaluation will also include the generic quality of life instrument, the EuroQol EQ-5D-5L (EuroQol 1990).

Completion date
01/07/2023

Reason abandoned (if study stopped)
Participant recruitment issue

Eligibility

Key inclusion criteria
1. Participant is willing and able to give informed consent for participation in the study
2. Patient is willing and able to follow pre and post-operative follow up in Oxford
3. Male or female, aged 18 years or above
4. Participants are diagnosed as having probable chronic post-stroke pain of 2 years' minimum duration refractory to at least 1 opiate medication, 1 anti-epileptic and 1 anti-depressant, AND mean usual VAS pain score > 7/10 despite input from a multidisciplinary pain team

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Contraindication for elective general anaesthesia, for example severe cardiovascular disease
2. Contraindication to MRI
3. Contraindication to neurosurgery, eg. Bleeding disorders, not able to stop anticoagulation

safely for perioperative phase (approx. 10 days)
4. Major psychiatric or cognitive disorder that may affect capacity
5. Active skin based infection or colonisation with a multi-drug resistant organism e.g. MRSA
6. Patient requiring regular MRI investigations postoperatively
7. Patient likely to require diathermy, ultrasound or transcranial magnetic stimulation post DBS device insertion.
8. Patient not tolerant of awake surgery
9. Participant not demonstrating adequate response to stimulation in stage 1 surgery
10. Patient unable to cooperate with device recharging
11. Pregnancy or planned pregnancy

Date of first enrolment
01/03/2020

Date of final enrolment
01/03/2022

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Oxford University Hospitals NHS Foundation Trust
John Radcliffe Hospital
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Sponsor information

Organisation
University of Oxford

Funder(s)

Funder type
Charity

Funder Name
The Jon Moulton Charity Trust (Guernsey)

Results and Publications

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Participant information sheet		17/09/2019	10/01/2020	No	Yes