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Diabetic peripheral neuropathy treatment with dorsal root ganglion stimulation – the PENTAGONS trial

Submission date
01/10/2018

Recruitment status
Stopped

Registration date
08/10/2018

Overall study status
Stopped

Last Edited
25/11/2024

Condition category
Nervous System Diseases

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

Plain English summary of protocol

Background and study aims
A common complication of diabetes is damage to the nerves in the limbs, known as diabetic neuropathy. This often causes pain, commonly in the feet. Pain can be severe, and may not be adequately controlled by medication. This study tests a treatment called Dorsal Root Ganglion Stimulation (DRGS) for painful diabetic neuropathy (PDN) of the feet. In DRGS, a system is implanted that delivers small electrical current pulses to stimulate the nerves that are carrying pain signals from the feet at the point where they enter the spine. At this point there is a small swelling on the nerve called the dorsal root ganglion and it is this that is stimulated. DRGS has proved effective for similar types of pain in the lower limbs that is due to other causes. Implantation is performed in two stages: first, wires are inserted into the low back through hollow needles. Each wire tip is positioned in contact with a dorsal root ganglion. Second, the wires are connected to a pulse generator implanted just under the skin, which contains a battery and electronics to generate stimulus pulses, similar to a heart pacemaker. The aim of this study is to find out how effective DRGS is as a treatment for PDN, and whether DRGS improves foot perfusion (blood flow) in patients with PDN.

Who can participate?
Patients aged 18 or above with severe PDN that is not adequately controlled by medication

What does the study involve?
After an assessment of pain levels and quality of life, participants are randomly allocated to either undergo insertion of a DRGS system, or continue on treatment with medication alone. The participants' pain levels and quality of life are reassessed over the following 6 months to see if DRGS is effective in treating PDN. In some of the participants tests are performed to examine the effects of DRGS on nerve function and blood flow, which are both abnormal in PDN.

What are the possible benefits and risks of participating?
If the treatment is successful, then participants in the DRGS group will benefit from pain relief. DRGS is a surgical procedure and as would be expected it carries risks. These include infection of the implant; failure of the treatment due to displacement of the implanted stimulator wire from

its target, which may require replacement of the wire; leakage of spinal fluid; nerve damage; and the procedure uses x-rays which can be damaging to a developing baby and therefore pregnant patients will not be able to participate.

Where is the study run from?
1. University of Oxford (UK)
2. South Tees Hospitals NHS Foundation Trust (UK)
3. University Hospital Southampton NHS Foundation Trust (UK)
4. Salford Royal NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
June 2018 to June 2020

Who is funding the study?
Abbott Laboratories (USA)

Who is the main contact?
Ms Jo Cook
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
CPMS 37188

Study information

Scientific Title
Diabetic peripheral neuropathy treatment with dorsal root ganglion stimulation: a randomised controlled trial

Acronym
PENTAGONS

Study objectives
Main research questions:
1. How effective is dorsal root ganglion stimulation (DRGS) as a treatment for painful diabetic neuropathy (PDN)?
2. Does DRGS improve foot perfusion in patients with PDN?

Ethics approval required
Old ethics approval format

Ethics approval(s)
South Central - Oxford C Research Ethics Committee, First MREC approval date 09/05/2018, ref: 18/SC/0146

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

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
See study outputs table

Health condition(s) or problem(s) studied
Painful diabetic neuropathy

Interventions
This is an open label randomised trial of surgery versus continued medical management. The expected duration of participant participation is 8 to 10 months from the point of consent.

Potential participants will be identified through specialist clinics in pain and diabetology, and vascular surgery. They will be approached by the medical staff within the clinic and provided with a PIS with permission for a member of the study team to contact them by telephone to discuss the study. If they are interested in participating they will be seen in the neuromodulation clinic and screened by review of history and medical records and clinic appointment for suitability for DRGS. Those meeting the inclusion and exclusion criteria will be invited to enroll.

If they accept this invitation they will have an MRI scan of the low back to ensure that there is no significant narrowing of the space around the nerves where the wires are to be inserted, and they will undergo baseline assessments with questionnaires that assess pain, quality of life and medication use.

Participants will then be randomised in a 1:1 ratio to either receive DRGS or continue on their medical treatment.

Participants undergoing DRGS will have preoperative assessments in line with routine clinical practice. This includes a preoperative health check for safety purposes which involves physical examination, blood tests, and an electrocardiogram. Participants will be excluded from surgery if there are any safety concerns.

Surgery to implant the stimulator system will then take place in the participants randomised to have DRGS. Wires are inserted into the lower back through a needle. This procedure is similar to the procedure for giving an epidural anaesthetic (as used for example for pain relief in childbirth). The wires are then connected to a ‘pulse generator’ that is implanted under the skin. The pulse generator is a small box rather like a heart pacemaker, which contains a battery and some electronics to generate small pulses of electricity that pass down the wires to electrical contacts at the wire tip, where they continuously stimulate the DRG. The procedure typically takes between 45 and 90 minutes although some cases may take longer. It is performed under local anaesthesia, with sedation to ensure that the patient is comfortable.

All participants will be followed up three times, on each occasion completing the same questionnaires as at baseline. The follow up timepoints will be 2, 12, and 24 weeks postoperatively in the DRGS arm; surgery will occur 6 weeks post randomisation and thus the corresponding timepoints in the continued medical management (CMM) arm will be 8, 18, and 30 weeks post-randomisation.

Participation ends after the final follow up appointment. Participants with implants will have indefinite clincial follow up thereafter by the direct care team in line with that provided for

routine clinical DRGS for any other indication. In the event that the trial results are positive, the participants in the non-surgical group will subsequently be offered surgery.

A subset of participants in both surgical and non-surgical groups (numbering 10-12 per group) will be invited to participate in a substudy, in which they will undergo testing to investigate the effects of stimulation on nerve function and blood flow in the feet. This will involve measuring their threshold for sensing warmth, cold, and vibration stimuli, measuring activity in nerve fibres that control functions such as sweating and blood flow, and directly measuring blood flow and oxygen levels in the skin. This testing will be done at the same timepoints as the questionnaires completed by all participants. Because of the requirement for specialist equipment, this will be at the lead centre only. Potential participants at this centre will be provided with an additional PIS for the substudy and if the participant wishes to participate an additional ICF will be completed. It will be made clear that participation in the substudy is entirely optional, and in particular that participation in the main study will not be affected by whether they wish to participate in the substudy.

Intervention Type
Procedure/Surgery

Primary outcome measure
Pain is measured using the visual analogue scale (VAS) at baseline and 30 weeks post randomisation

Secondary outcome measures
1. Pain is measured using the visual analogue scale (VAS) at 8 and 18 weeks post randomisation
2. Pain is measured using the neuropathic pain symptom inventory (NPSI) at baseline and 8, 18, and 30 weeks post randomisation
3. Pain is measured using the brief pain inventory (BPI) at baseline and 8, 18, and 30 weeks post randomisation
4. Quality of life is measured using the Euroqol EQ-5D-5L at baseline and 18 and 30 weeks post randomisation
5. Sleep quality is measured using the Medical Outcomes Study (MOS) sleep scale at baseline and 18 and 30 weeks post randomisation
6. Affective symptoms are measured using the Hospital Anxiety and Depression Scale (HADS) at baseline and 18 and 30 weeks post randomisation

Overall study start date
13/06/2018

Completion date
12/06/2021

Reason abandoned (if study stopped)
Participant recruitment issue

Eligibility

Key inclusion criteria
Current inclusion criteria as of 17/12/2018:
The participant may enter the trial if ALL of the following apply:
1. Participant is willing and able to give informed consent for participation in the trial

2. Male or Female, aged 18 years or above
3. Diagnosed with PDN of the feet, present for at least 6 months and scoring at least 50mm on a pain VAS despite medical treatment
4. Score of at least 2 out of 10 using the Michigan Neuropathy Screening Instrument for peripheral neuropathy (see Appendix D)
5. Participant has tried at least two first-line pharmacotherapy options and either is refractory to painkilling medication, or the required dose of medication to alleviate pain causes severe side effects. These should include at least one antiepileptic (gabapentin or pregabalin), and at least one antidepressant (amitriptyline or duloxetine)
6. Stable analgesic medication regimen for at least 4 weeks prior to trial entry. This includes patients not taking analgesics at all (either because they are refractory, or because side effects are too severe)
7. Female participants of child bearing potential must be willing to either state prior to enrolment that there is no chance that they could be pregnant, or if there is a chance that they might be pregnant, to undergo a pregnancy test. This is because the insertion of a DRGS system requires X-ray fluoroscopy that might be harmful to a developing foetus
8. If, in the Investigator's opinion, the patient is able and willing to comply with all trial requirements
9. If, in the opinion of a consultant anaesthetist after review of case notes and medical history, there are no contraindications to DRGS surgery
10. Willing to allow his or her General Practitioner and consultant, if appropriate, to be notified of participation in the trial

Previous inclusion criteria:
The participant may enter the trial if ALL of the following apply:
1. Participant is willing and able to give informed consent for participation in the trial
2. Male or Female, aged 18 years or above
3. Diagnosed with PDN of the feet, present for at least 6 months and scoring at least 50mm on a pain VAS despite medical treatment
4. Score of at least 2 out of 10 using the Michigan neuropathy screening instrument for peripheral neuropathy (see Appendix C)
5. Participant has tried at least two first-line pharmacotherapy options and either is refractory to painkilling medication, or the required dose of medication to alleviate pain causes severe side effects. These should include at least one antiepileptic (gabapentin or pregabalin), and at least one antidepressant (amitriptyline or duloxetine)
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Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 56; UK Sample Size: 56

Total final enrolment
2

Key exclusion criteria
Current exclusion criteria as of 17/10/2019:
The participant may not enter the trial if ANY of the following apply:
1. Female participant who is pregnant or planning pregnancy during the course of the trial.
2. Lack of good understanding of both written and spoken English. Most of the outcome measures, including the primary outcome measure, are in the form of questionnaires and these require good understanding of written English in order to provide valid measures. Fluent spoken English is needed during the implantation procedure when the participant is asked to confirm that the stimulation effect can be felt in the painful area.
3. Active infection other than viral infections that are mild and confidently expected to be self-limiting within two weeks (e.g. common colds)
4. Anticoagulant treatment or other coagulopathy
5. Diabetic ulcers at the time of, or in the 3 months prior to, recruitment
6. Participant rates their pain consistently as 10 out of 10, even on their best day. This indicates a failure to understand the principles of VAS use, or pain catastrophisation, either of which will confound pain scoring
7. Significant pain elsewhere in the body from any condition, which the participant is not easily able to rate separately from their foot pain. Participants must be able to clearly rate their foot pain alone and will be excluded if in the opinion of the Investigator they are unable to do so
8. Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participant at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial
9. Opiate use greater than the maximum recommended amount for non-cancer pain (120mg morphine or equivalent per 24 hours)
10. Participation in a clinical trial of an investigational medicinal product (CTIMP) in the past 12 weeks
11. Previous lumbar spine surgery at or below the level of the third lumbar vertebra (L3). This is because the scarring following lumbar spine surgery frequently makes it impossible to pass a DRG wire
12. Previous failed Spinal Cord Stimulation therapy or other neuromodulation treatment
13. Previous lumbar or sacral radiofrequency nerve lesioning
14. Inability to have a preoperative MRI scan, either due to claustrophobia or due to the presence of a contraindication to MRI scanning
15. A previously performed MRI scan shows a contraindication to DRG lead insertion (if previous MRI scans are available they should be reviewed at this stage, prior to randomisation, to confirm no contraindication is present)

16. Body Mass Index (BMI) > 30
17. Patient is undergoing psychological therapy

Previous exclusion criteria as of 17/12/2018:
The participant may not enter the trial if ANY of the following apply:
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12. Previous failed Spinal Cord Stimulation therapy or other neuromodulation treatment
13. Previous lumbar or sacral radiofrequency nerve lesioning
14. HbA1c greater than 8.5% or 69.4 mmol/mol, at last check, in order to exclude very poorly controlled disease. This is in line with national guidelines for the maximum HbA1c recommended in diabetic patients undergoing elective surgery. HbA1c will be checked routinely at preoperative assessment for those randomised to the DRGS group, but for screening purposes prior to randomisation, the value from the last check done at the diabetic clinic or GP surgery should be obtained
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15. Inability to have a preoperative MRI scan, either due to claustrophobia or due to the presence of a contraindication to MRI scanning
16. Patient is undergoing psychological therapy

Date of first enrolment
21/01/2019

Date of final enrolment
31/10/2020

Locations

Countries of recruitment
England

United Kingdom

Study participating centre

Nuffield Department of Surgical Sciences
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Study participating centre
South Tees Hospitals NHS Foundation Trust
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Sponsor type
University/education

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Industry

Funder Name
Abbott Laboratories

Alternative Name(s)
Abbott, Abbott U.S., Abbott Alkaloidal Company

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Publication and dissemination plan
Current publication and dissemination plan as of 25/11/2024:
No publication is planned due to low recruitment and lack of data.

Previous publication and dissemination plan:
Planned publication in a high-impact peer-reviewed journal in the first half of 2021.

Intention to publish date

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are not expected to be made available due to low recruitment and lack of data.

IPD sharing plan summary

Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version V5.0	04/12/2018	17/10/2019	No	Yes
Protocol file	version V4.0	31/07/2019	17/10/2019	No	No
HRA research summary			28/06/2023	No	No