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External peripheral nerve stimulation for the treatment of neuropathic pain following nerve injury

Submission date
23/05/2016

Recruitment status
No longer recruiting

Registration date
07/07/2016

Overall study status
Completed

Last Edited
09/11/2021

Condition category
Nervous System Diseases

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Eight percent of people in the United Kingdom are estimated to have persistent (chronic) neuropathic (nerve) pain. Medications are the most common treatment method but often have limited benefit or unwanted side effects. Surgical treatments such as spinal cord stimulation (implantation of a device which applies an electrical current to the spine to relieve pain) are then often considered. External non-invasive peripheral nerve stimulation (EN-PNS) is a form of electrical stimulation that involves placing a pen shaped electrode onto the skin, which can be easily self-administered by patients. It has been found that EN-PNS can provide significant pain relief for people with neuropathic pain in a particular area (localized), however there is currently no evidence to support its use within the National Health Service (NHS). The aim of this study is to find out whether EN-PNS is effective in reducing pain for people with long-standing neuropathic pain following damage to the nerves that connect to the brain and spinal cord (peripheral nerve injury).

Who can participate?
Adults with long-standing (at least 12 months) neuropathic pain following peripheral nerve injury

What does the study involve?
Participants are randomly allocated to receive one of two forms of EN-PNS treatment (both forms of EN-PENS will look the same however the stimulation frequency will differ). Participants are trained to deliver their own treatment over 1-3 sessions over the period of one week, before being asked to continue treatment themselves at home. Participants are able to choose how often they use the treatment, but it must be for at least 10 minutes once a day. At the end of this home treatment phase participants will have the option to have a further three months treatment extension, a three month switch to the use the device the other group used, or to end the trial. Participants in both groups complete a number of questionnaires at the start of the study and then after three months to measure their pain levels, emotional and physical functioning and quality of life.

What are the possible benefits and risks of participating?
Not provided at time of registration

Where is the study run from?
The Walton Centre NHS Trust (UK)

When is the study starting and how long is it expected to run for?
June 2016 to May 2020

Who is funding the study?
National Institute for Health Research (UK)

Who is the main contact?
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Contact information

Type(s)
Public

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Additional identifiers

Protocol serial number
PB-PG-0215-36039

Study information

Scientific Title
A randomised patient-assessor blinded controlled trial of External non-invasive peripheral nerve stimulation for chronic neuropathic pain following peripheral nerve injury (EN-PENS)

Acronym
EN-PENS

Study objectives
EN-PNS can provide effective pain reduction for people with chronic neuropathic pain following a peripheral nerve injury.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Northwest- Preston Research Ethics committee, 29/04/2016, ref: 16/NW/0273

Study design
Randomised patient-assessor blinded controlled parallel-group two-arm superiority add-on trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Neuropathic pain following peripheral nerve injury

Interventions
Patients will be randomised to receive one of two forms of EN-PENS treatment (xavant stimpod NMS460 or control) by an independent randomisation service via an online system based at the King's Clinical Trials Unit (King's CTU) based at the Institute of Psychiatry. Randomisation will use a 1:1 allocation by a computer generated randomisation schedule (concealed). Blocking will be used to ensure a balance between the numbers in the two groups throughout recruitment. Varying block sizes will be used.

Participants in both arms are trained to deliver their own treatment over 1-3 sessions in which they receive 5 minutes of stimulation (these sessions will be delivered within the period of 1 week). They will then continue treatment for 3 months at home where they will determine their own treatment frequency (minimum of 1x day for 10 minute period).

Xavant stimpod NMS460: A frequency of 2Hz, pulse width 1.0 ms and maximal amplitude of 30mA will be used to deliver stimulation via a ball shaped electrode. The electrode shape creates a high current density which when used in combination with the specified stimulation parameters achieves analgesia through a specific mechanism, preferential activation of superficial nociceptive A-delta fibres inducing long-term depression (LTD) of synaptic strength.

Control: The machine will look identical and use the same frequency (2 Hz). A square flat shaped TENS electrode, a pulse width of 0.1ms delivered at a maximum current of 6mA will be used with the control device; this will produce a lower current density/intensity not activating small fibres. The display will appear to allow patients the same freedom to increase stimulation on both machines to 30mA; however the control devices delivered maximal output will be limited to 6mA.

Participants are followed up at the end of the home treatment phase (12 weeks). At the end of the home treatment phase participants will have the option to have a further 3 months treatment extension, 3 month switch to the opposite treatment arm, or to end the trial.

Intervention Type
Device

Phase
Not Applicable

Primary outcome(s)
Average 24 hour pain intensity recorded on an 11-point (0-10) numerical rating scale, averaged over the last 7 days of the 3 month home-loan period.

Key secondary outcome(s))
1. Quality of life is measured using the EuroQOL-5D-5L questionnaire at baseline, 1, 2 and 3 months and end of where applicable end of optional treatment extension/swap (6 months)
2. Physical function will be assessed using the Brief Pain Inventory questionnaire interference subscale at baseline and 3 months

Exploratory Outcomes:
1. Emotional functioning is measured on the Hospital Anxiety and Depression Scale questionnaire at baseline and 3 months
2. Perceived control in terms of confidence in being able to perform day to day tasks despite pain is measured using the pain self-efficacy questionnaire at baseline and 3 months
3. Surface area of allodynia is measured in cm2 using a brush to identify the boundaries of the affected area (a washable marker pen will mark an outline of the boundaries and this will be traced onto clear plastic acetate) at baseline and 3 months
4. The intensity of allodynia will be measured on a numerical rating scale (NRS), as the average of 3 strokes across the allodynic area, during study screening
5. Quality of pain is measured using the neuropathic pain symptom inventory (NPSI) questionnaire at baseline and 3 months
6. A specially designed optional sensory test will be conducted for patients who consent to this at 3 months which will help aid understanding of the working mechanisms of treatment
7. Health economic analysis – will be conducted using self-reported measures of health care utilisation and EuroQOL-5D-5L at baseline and 3 months
8. Potential medical suitability for invasive NeuroModulation will be determined by review of case notes and clinic letters by a pain and neuromodulation consultant

Completion date
16/01/2020

Eligibility

Key inclusion criteria
1. Chronic neuropathic pain following peripheral nerve injury, definite or probable:
1.1. Pain with a distinct neuroanatomically plausible distribution
1.2. A history suggestive of a relevant lesion or disease affecting the peripheral or central somatosensory system
1.3. Demonstration of the distinct neuroanatomically plausible distribution by at least one confirmatory test
1.4. Demonstration of the relevant lesion or disease by at least one confirmatory test
Grading of certainty for the presence of neuropathic pain: definite neuropathic pain: all (1 to 4); probable neuropathic pain: 1 and 2, plus either 3 or 4 (Treede, Jensen et al. 2008)
2. At least 12 months duration of neuropathic pain symptoms
3. Adults age 18 years or above
4. Moderate to severe pain intensity (Average 24 hour pain intensity over 7-days at baseline of ≥ 5/10 but not dropping below 4 on any single day, on an 11-point (0-10) numerical rating scale

(NRS))
5. Pain localised to the distribution of 1-2 peripheral nerves
6. Distribution of pain that will allow for the nerve to be stimulated proximally from the areas of pain.
7. Discontinuation of numbing pain medications (lidocaine patches 4 weeks prior, Capsaicin 4 months prior)
8. Patients should have trialed first line pharmacotherapy (First-line treatment include either tricyclic antidepressants or serotonin-noradrenaline reuptake inhibitors, pregabalin or gabapentin)
9. Moderate- severe brush stroke allodynia (Defined as pain of ≥ 5/10 on an 11-point (0-10) numerical rating scale (NRS), when brush stroke is applied to the affected area (average of 3 strokes over affected area))
10. Willing to not commence any new medications/ treatments for their neuropathic pain whilst involved in the trial
11. Women of childbearing potential may participate providing they are using adequate birth control methods for the duration of the trial (including accepted methods of contraception such as; barrier methods, intrauterine device IUD, contraceptive implant, depot injection, oral contraception and abstinence (as part of lifestyle choice))

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
76

Key exclusion criteria
1. Absolute numbness within area of pain (suggests sufficient nerve damage to render EN-PNS unlikely to work)
2. Known EN-PNS contraindications (pregnancy and cardiac pacemakers)*
3. Other chronic pains or unstable medical conditions, which in the opinion of the investigator would make the trial unsuitable for the patient
4. Unstable pain intensity or pain medications 6 weeks prior to the study that in the judgement of the PI would interfere with assessment of outcome
5. Persons participating in an interventional trial within the past 3 months
6. Persons participating in a non-interventional trials completed within 2 weeks prior to start of the trial
7. Diagnosed psychiatric or mental health disorder which in the judgment of the PI interferes with successful study participation
8. Inability to comply with the study protocol for the trial-period of 3 months

9. Inability to complete outcome measures
10. Incapacity to understand the information necessary to provide informed consent
11. Other implanted device for the same pain complaints such as spinal cord stimulation (SCS)
12. Phantom Limb pain**

*Non pregnancy confirmed by urine test at baseline and at treatment end
**Stump pain can be treated

Date of first enrolment
01/02/2018

Date of final enrolment
18/07/2019

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
The Walton Centre NHS Trust
Lower Lane
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L9 7LJ

Sponsor information

Organisation
The Walton Centre NHS Trust

ROR
https://ror.org/05cvxat96

Funder(s)

Funder type
Government

Funder Name

National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
Requests for patient-level data and statistical code should be made to the corresponding authors and will be considered by members of the study teams, including the study PIs and the sponsor sites neuroscience research unit (NRU) on a case-by-case basis. Access will be provided to researchers after the proposal has been reviewed and agreed by the sponsor sites data sharing committee, and the trusts IG department, beginning 3 months and ending 5 years following article publication. The data will not contain any direct identifiers, we will minimise indirect identifiers and remove free text data to minimise the risk of identification.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		06/11/2021	09/11/2021	Yes	No
Protocol article	protocol	06/12/2016		Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes