ISRCTN70120536 https://doi.org/10.1186/ISRCTN70120536

Research into the changes of immune cells in spinal fluid after treatment with amitriptyline and spinal cord stimulation in neuropathic pain

Submission date
25/07/2017

Recruitment status
No longer recruiting

Registration date
12/09/2017

Overall study status
Completed

Last Edited
11/10/2023

Condition category
Signs and Symptoms

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

Plain English summary of protocol

Background and study aims
This is a study to explain how the drug amitriptyline and spinal cord stimulators treat nerve pain. It is thought that immune cells are responsible for a lot of the symptoms of nerve pain. The aim is to sample spinal fluid which contains immune cells and compare them before and after treatment.

Who can participate?
Patients aged 20 – 65 with nerve pain (study 1) and who have been implanted with a spinal cord stimulator (study 2)

What does the study involve?
A sample of spinal fluid is taken. Participants in study 1 are then treated with amitriptyline and participants in study 2 are treated with spinal cord stimulation. After treatment a second sample of spinal fluid is taken to compare the immune cells before and after treatment.

What are the possible benefits and risks of participating?
There are no benefits to this study for patients other than contribution to science. Participants are offered the treatments regardless of whether they participate in the study. There is a risk of infection, bleeding, nerve damage and headache related to pain procedure and spinal fluid sampling. However, this is rare. The methods used are well established in the St. James Pain Medicine unit and have already been demonstrated to be safe. Amitriptyline has some side effects like drowsiness and dry mouth.

Where is the study run from?
St James's Hospital (Ireland)

When is the study starting and how long is it expected to run for?
April 2017 to March 2018

Who is funding the study?
Haughton Institute (Ireland)

Who is the main contact?
Dr Jonathan Royds

Contact information

Type(s)
Public

Contact name
Dr Jonathan Royds

ORCID ID
https://orcid.org/0000-0003-0756-2690

Contact details
Dept of Pain Medicine
St James's Hospital
Dublin
Ireland
8

Additional identifiers

Protocol serial number
2016-12 List 47(7)

Study information

Scientific Title
Characterisation of the peptide and cellular constituents of cerebrospinal fluid implicated in the chronicity of neuropathic pain in vivo and its response to treatment with amitriptyline and neuromodulation

Study objectives
Amitriptyline and Spinal Cord Stimulation are currently the most effective analgesic therapies in the management of chronic neuropathic pain. Published research supports the hypothesis that their mechanism of action occurs centrally. This research will examine the effect of amitriptyline and spinal cord stimulation on peptides and immune cells in the cerebrospinal fluid of patients with chronic neuropathic pain. A more detailed characterisation of the effects of both therapies on the central peptides and immune cells will facilitate better stratification and optimisation of currently employed therapies as well as providing information which may facilitate the addition of new therapies such as immune inhibitor drugs in the management of chronic neuropathic pain.

Ethics approval required
Old ethics approval format

Ethics approval(s)

Tallaght Hospital and St James's Hospital Research Ethic Committee, 23/12/2016, REC ref: 2016-12 List 47 (7) and (8)

Primary study design
Interventional

Study design
Study 1: interventional observational pilot study
Study 2: interventional pilot study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Chronic lumbar radicular pain, failed back surgery syndrome, complex regional pain syndrome

Interventions
Study 1: Amitriptyline study
This is an interventional observational pilot study to determine the effects of amitriptyline on neuropeptides, lymphocytes and non-lymphocyte constituents in the CSF. It will also observe the effects of selective nerve root blocks and amitriptyline on patient's pain and function. Patients will complete visual analogue pain (VAS) and DN4 neuropathic pain questionnaires before and after amitriptyline and intervention. The second set of pain scores will be taken prior to additional sampling of CSF. Analgesic consumption will also be analysed before and after amitriptyline. Patients with a diagnosis of lumbo-sacral radicular pain will be offered inclusion in this study if they wish after a period of reflection. They will be treated with a selective nerve root block (SNRB) as is the common standard practice and have a baseline CSF taken during this procedure. Efficacy of the SNRB can be verified after the procedure using VAS. They will then be commenced on amitriptyline for 8 weeks prior to treatment with pulsed radiofrequency (PRF) if the SNRB was successful. A second sample of CSF will again be taken prior to PRF 6-8 weeks later. This will provide a baseline sample and sample after treatment with amitriptyline.

Study 2: Neuromodulation study
This is a interventional pilot study to determine the effects of different waveforms (conventional, HF 10KHZ and burst) of spinal cord stimulation on neuropeptides, lymphocytes and non-lymphocyte constituents in the CSF. It will also assess the impact of spinal cord stimulation on pain and function. Patients will complete visual analogue pain (VAS) and DN4 neuropathic pain questionnaires before and after the designated spinal cord stimulation. Patients with a diagnosis of failed back surgery syndrome or CRPS and have a functioning spinal cord stimulator will be offered inclusion in this study. After a period of reflection, having been given a patient information leaflet and 3 months after implantation, they will have CSF sampled using different modes of stimulation: conventional, burst and high frequency.

Lumbar Puncture
A sterile lumbar puncture will be performed in the sitting position with a 25 Gauge Whitacre needle following skin infiltration with 2ml 1% lidocaine. CSF will be allowed to drain from the needle until the fluid is clear of visible blood staining. A 1.5 ml sample of CSF will be collected in TransFix/EDTA CSF Sample Storage Tubes (Caltag, UK) which are specifically designed for the stabilisation of cells within CSF specimens. 1.5 ml of CSF will be frozen immediately for analyte analysis.
CSF samples will be taken immediately before the SNRB/DRG block. The CSF samples will be

centrifuged to isolate the cellular content and the cells will be stained with anti-human antibodies including CD3, CD4, CD8, CD56, panγδ, CD14 and CD19. To assess activation status of the immune cells, cells will be labeled with markers including CD69, CD45RO, CD45RA and CD62L. To identify the role of these cells in neuroinflammation, cells will be permeabilised and labeled with antibodies against inflammatory cytokines including TNF-α, IL-1β, IL-6, IFN-γ, IL-10 and IL-17. Cells will be acquired using a Beckman Coulter Cyan ADP flow cytometer and analysed using FlowJo V7 software. Samples will be analysed for NGF, BDNF, VEGF and MCP-1 using single and multiplex ELISAs and samples will also be assessed by mass spectrometry.
In vitro studies will examine the direct effect of amitriptyline on activated T cells. T cells will be isolated from PBMCs using Ficoll Paque and density centrifugation. T cells will be activated using 1µg/ml of anti-CD3 (eBioscience) and 1µg/ml anti-CD28 (eBioscience). Cells will be culture at 5x105/ml and cultured in a concentration range of amitriptyline with clinical relevance. T cell activation, survival and cytotoxic function will be assessed by flow cytometry to assess cell cycle, apoptosis, cytokine and CD107a expression. All of these techniques are optimised and used regularly in laboratory.

Protocol for Mass Spectrometry:
See attached MS Core facility protocol. The mass spectrometry will be carried out with Systems Biology Ireland in UCD as they are leading experts in this technology and will help with any optimisation required for CSF sample prep and analysis.

Intervention Type
Procedure/Surgery

Primary outcome(s)
Frequency of neuroimmune cells CD4+ T Cell, CD8+ T Cells, and Natural Killer cells in the cerebrospinal fluid, assessed by flow cytometry before and after treatment with amitriptyline (study 1) and spinal cord stimulation (study 2).

The exact date after recruitment will be after at least 2 weeks for reflection. With study 1 the second sample will be taken 6-8 weeks after treatment with amitriptyline. In study 2 the second sample will be taken after 2 weeks of neuromodulation.

Key secondary outcome(s)
1. Changes in neuropeptides and cytokines commonly associated with chronic neuropathic pain conditions (BDNF, Substance P, NGF, MCP-1, VEGF, IFN-gamma, IL-1, IL-6, TNF α), assessed by flow cytometry, single and multiplex ELISAs and mass spectrometry before and after treatment with amitriptyline (study 1) and spinal cord stimulation (study 2)
2. Pain, measured using visual analogue pain scores and DN4 neuropathic pain questionnaires, and analgesic consumption before and after treatment with amitriptyline (study 1) and spinal cord stimulation (study 2)

The exact date after recruitment will be after at least 2 weeks for reflection. With study 1 the second sample will be taken 6-8 weeks after treatment with amitriptyline. In study 2 the second sample will be taken after 2 weeks of neuromodulation.

Completion date
30/03/2018

Eligibility

Key inclusion criteria
Amitriptyline study:
1. Patients aged 20 – 65 years with lumbar radicular pain
2. Clinical and radiological evidence of one nerve root and/or dermatome affected

Neuromodulation study:
1. Patients aged 20 – 65 years with FBSS or CRPS who have been implanted with a spinal cord stimulator

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Key exclusion criteria
Amitriptyline study:
1. Patient refusal
2. Anticoagulant medication
3. Infection
4. Pregnancy
5. Breastfeeding
6. Corticosteroid therapy
7. Stroke
8. Psychiatric history
9. History of ischaemic heart disease
10. Arrhythmia
11. Heart block
12. Cerebral impairment
13. Current anti-neuropathic medication
14. Biologic medication

Neuromodulation study:
1. Patient refusal
2. Anticoagulant medication
3. Infection
4. Pregnancy
5. Breastfeeding
6. Corticosteroid therapy
7. Stroke
8. Psychiatric history
9. Cerebral impairment
10. Biologic medication

Date of first enrolment

01/04/2017

Date of final enrolment
30/01/2018

Locations

Countries of recruitment
Ireland

Study participating centre
St James's Hospital
Dublin
Ireland
8

Sponsor information

Organisation
St James's Hospital / Trinity College Dublin

ROR
https://ror.org/04c6bry31

Funder(s)

Funder type
University/education

Funder Name
Haughton Institute

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Dr Jonathan Royds.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		01/01/2021	11/10/2023	Yes	No
Participant information sheet		12/09/2017	12/09/2017	No	Yes
Participant information sheet		12/09/2017	12/09/2017	No	Yes