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PRIMA – Pain relief in major amputation

Submission date 09/07/2021	**Recruitment status** No longer recruiting	[ ] Prospectively registered [ ] Protocol
Registration date 21/07/2021	**Overall study status** Completed	[ ] Statistical analysis plan [ ] Results
Last Edited 02/02/2022	**Condition category** Surgery	[ ] Individual participant data [ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Major lower limb amputation, (MLLA) are commonly performed operations by Vascular Surgeons; over 3000 each year. At present there lacks a universally accepted method of pain relief for these patients. Phantom limb pain is a recognised common problem; the best way to achieve good pain relief is to use a variety of methods but practice and experience is variable. One method is to inject the nerve's coating (perineural sheath) with a local anaesthetic before surgery has started (single shot nerve block) another is to place a catheter into this sheath (perineural catheter or PNC) to deliver a continuous infusion of local anaesthetic for up to 7 days post operatively.
This study will compare these two methods to find out which results in less post-operative pain for our patients.

Who can participate?
Eligible patients are anyone undergoing a primary above/below knee amputation under general anaesthetic for the symptoms resulting from peripheral vascular disease, aged over 18 years old. They need to be able to consent to amputation and study participation and to participate in assessing their pain using pain scores and assessment questionnaires.

What does the study involve?
The participants will be involved in the study for 6 weeks. They will fill out daily pain scores for the first week, phantom limb score and two quality of life questionnaires pre-op and at day 7 and at their usual 6 week outpatient clinic follow up. Physiotherapists will document daily progress for the first week. We intend to gain funding to review these patients at a year to detect difference in long-term phantom pain.

What are the possible benefits and risks of participating?
There are no specific issues. The two therapies are at present, both offered locally and nationally but there is no evidence as to which is superior. There are concerns that patients who undergo amputation without effective pain control become reliant on opioid mediation. This of course carries with it significant risks of long-term dependence and may lead to falls or overdose.

Where is the study run from?
Freeman Hospital (UK)

When is the study starting and how long is it expected to run for?
May 2021 to May 2023

Who is funding the study?
Royal College of Surgeons of Edinburgh (UK)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Integrated Research Application System (IRAS)
271797

Central Portfolio Management System (CPMS)
48308

Protocol serial number
Grant Codes: SRG/19/131

Study information

Scientific Title
Pain Relief in Major Amputation (PRIMA): A randomised clinical trial comparing pre-incision ‘single-shot’ nerve block and continuous peri-neural catheter for patients undergoing a major lower limb amputation

Acronym
PRIMA

Study objectives
The null hypothesis of this study is that "no difference in post-procedural pain scores exist between patients who have undergone a single shot nerve block when compared to patients who have had a nerve catheter infusion running for 7 days.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 24/06/2021, South East Scotland REC 1 (2ndFloor, Waverley Gate, 2-4 Waterloo Place, Edinburgh, EH1 3EG, UK; +44 (0)7814 764 241; Sandra.Wyllie@nhslothian.scot.nhs.uk), ref: 21/SS/0013

Primary study design
Interventional

Study design
Interventional randomized controlled trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Pain relief in major amputation

Interventions
Participant pathway:
Patients who have a clinical indication for a major lower limb amputation (MLLA) and meet the inclusion/exclusion criteria will be invited to participate. MLLA can be a fairly urgent procedure so there is unlikely to be more than one or two days to discuss this study with the participant. Nonetheless, at the earliest opportunity following the plan for MLLA, patients will be reviewed by a member of the research study team. Here a patient information sheet will be given and the study and any questions will be discussed and answered. Thereafter during the next 12 - 24 hours, the patient will be consented to participate in the study.

Baseline documentation and questionnaires on pre-existing pain and current quality of life will then be completed.
The participant will then be randomised at this point to either method of pain control.

As per standard care, the participant will be consented by a member of the clinical team for their amputation. They will then head to theatre at their allocated time slot. The 'blocking' anaesthetist will be informed about the pain control method. They will then administer either the allocated single shot block or the nerve catheter.

The patient will then undergo the planned MLLA as per the standard operative procedure. The study team will collect data on the level of amputation, incision method to divide nerve, any additional local anaesthetic given along with the closure technique of the wound.

The techniques are detailed below.

Above Knee Amputation
Femoral Nerve Catheter
Equipment: Ultrasound Machine/Nerve Stimulator/Anaesthetic Prep Pack/Pajunk Tsui StimuLong Sono 50mm/100mm 18G Touhy needle and stimulating catheter
Technique: Patient asleep and supine, block area prepped with 0.5% chlorhexidine spray, operator scrubbed in sterile gown and gloves other appropriate PPE worn as required. Ultrasound probe covered with a sterile covering. Stop before you block performed. Leg scanned and femoral nerve identified. Incision to skin with a scalpel.
Touhy Needle inserted out of plane under ultrasound guidance with nerve stimulator set to 2.0 mA. Correct placement confirmed by patella twitch. Reduce current to threshold for loss of twitch if 0.2mA of less consider intra-neural placement and reposition. Once happy with needle position, note depth of needle at skin stimulate down the stimulating catheter at 1.5mA. Thread the catheter along the nerve until 4-6cm of catheter is next to the nerve ensuring no loss of twitch.
Load with 0.25% - 0.5% Levobupivacaine (Max total dose per patient 2.5-3 mg/kg). Tunnel to anterior abdominal wall and secure to skin. Apply filter.
Post-operatively connect to nerve catheter pump and run 0.1% bupivacaine at 10 ml/hr

Single Shot Sciatic Nerve Block
Equipment: Ultrasound Machine/100mm Block Needle
Technique: Patient asleep and in lateral or Sim's positon, block area prepped with 0.5% chlorhexidine spray, operator scrubbed in sterile gloves other appropriate PPE worn as required. Ultrasound probe covered with a sterile covering. Stop before you block performed. Leg scanned and sciatic nerve identified.
50mm-100mm block needle inserted in plane under ultrasound guidance. Load with 0.25% - 0.5% Levobupivacaine. Upto 20mls 0.5% levobupivacaine (Max total dose per patient 2.5-3 mg /kg).
Below Knee Amputation
Sciatic Nerve Catheter
Equipment: Ultrasound Machine/Nerve Stimulator/Anaesthetic Prep Pack/Pajunk Tsui StimuLong Sono 100mm 18G Touhy needle and stimulating catheter
Technique: Patient asleep and in Sim's position, (posterior approach to sciatic nerve/Labat's approach) block area prepped with 0.5% chlorhexidine spray, operator scrubbed in sterile gown and gloves other appropriate PPE worn as required. Ultrasound probe covered with a sterile covering. Stop before you block performed. Area scanned and Sciatic nerve identified. Incision to skin with a scalpel.
Touhy Needle inserted out of plane under ultrasound guidance with nerve stimulator set to 2.0 mA. Correct placement confirmed by plantar flexion of the foot/toes. Reduce current to threshold for loss of twitch if 0.2mA of less consider intra-neural placement and reposition. Once happy with needle position, note depth of needle at skin stimulate down the stimulating catheter at 1.5mA. Thread the catheter along the nerve until 4-6cm of catheter is next to the nerve ensuring no loss of twitch.
Load with 0.25% - 0.5% Levobupivacaine. Up to 20mls 0.5% levobupivacaine (Max total dose per patient 2.5-3 mg/kg). Tunnel to anterior abdominal wall and secure to skin. Apply filter.
Post-operatively connect to nerve catheter pump and run 0.1% bupivacaine at 10 ml/hr

Single Shot Femoral Nerve Block
Equipment: Ultrasound Machine/50mm Block Needle
Technique: Patient asleep and supine, block area prepped with 0.5% chlorhexidine spray, operator scrubbed in sterile gloves other appropriate PPE worn as required. Ultrasound probe covered with a sterile covering. Stop before you block performed. Leg scanned and femoral nerve identified.

50mm-100mm block needle inserted in plane under ultrasound guidance. Load with 0.25% - 0.5% Levobupivacaine. Up to 20mls 0.5% levobupivacaine (Max total dose per patient 2.5-3 mg /kg).

Surgical specifics

This is a pragmatic study and the operative procedure and technique will be left to surgeon preference. There are no specifications for nerve infiltration or nerve transection techniques although this data will be captured.

After the surgery, the patient will be returned to the ward or the post-operative recovery area, as determined by clinical need.

Once recovered from a general anaesthetic, the patient will at six to ten hours post operatively will be asked to complete the day of intervention pain diary. here they will be asked to draw a cross on a pain chart (likert scale) as to the level of pain they have.

On day 1 post operatively the patient's clinical care will continue unaltered. Complications including infection or return to theatre will be recorded in the patient record.

The patient will be asked to complete a daily pain diary at roughly the same time each day, this is a linear visual analogue scale.

Supplementary analgesia, opioid requirement and the 'number of button pushes' will be recorded. The pain team will document level of sedation and any nausea or vomiting the patient is experiencing. The physiotherapists will complete their own diary documenting patient's progress and engagement with physiotherapy.

These will all be completed daily over the next 7 days

On day 7 the, S-LANN (neuropathic pain assessment) and two Quality of life assessments SF36 and the EQ5D tool will be completed.

It is expected that most patients will be nearing discharge or step-down at approximately 7 days. The overall duration of admission to tertiary care, the need for further rehab and physio will be recorded.

After discharge and at 6 weeks (+/- 2 weeks) the participant will be invited for a routine follow-up visit. At this point there will be data collected on pain, wound healing, infection, night pain, pain scores, S-LANNS and QoL assessments.

The patient will be offered contact at one year telephone / postal contact, pending funding with the S-LANNS and SF36 QoL tool completed.

Randomisation

Prior to intervention, patients will be randomised to receive either a pre-incision ultrasound guided ‘single-shot’ perineural block or a PNC (perineural catheter), using computer-generated random permuted block randomisation in a 1:1 ratio.

Blinding

The nature of the intervention presents challenges for formal double-blinding without the use of complex ‘sham’ apparatus, even still patients are likely to be able to identify which intervention they have undergone by the lack/presence of a catheter penetrating the skin. There will be single blinding only of the trialists and data analysis team.

Sample size

A local observational study identified that those patients who received a single shot block had a Day 3 pain score of 4.8 compared to 1.2 for those who received a single-shot block. This is a 3.6

cm difference. The minimum clinically important difference is 13mm (95% CI 10-17mm, SD 18.3) on 100mm VAS 28.
In order to ensure we detect a difference and allowing for changes in the magnitude, the study has been powered to detect a 2.5cm difference with the PNC group having a pain score of 1.5 and the single-shot group having a pain score of 3.5 with a standard deviation of 2. The sample size is 14 patients per group to see this effect size with a power of 90% and alpha of 0.05. Accommodating a 20% attrition rate the total target sample size is 34 (17 per group).

Intervention Type
Procedure/Surgery

Primary outcome(s)
Post-operative pain (VAS) at day 3

Key secondary outcome(s)
1. Anaesthetic and operative times measured using patient records at a single time point
2. Adjunctive pain relief medication such as opioid use, tablets, patches and neuropathic medication measured using patient records at a single time point
3. Daily pain scores (VAS) from immediately post-operatively through to day seven
4. The duration of hospital stay measured using patient records at a single time point
5. Level of engagement and ability to participate in physiotherapy measured using an in-house developed two question physiotherapy tool, for the first seven days
6. The level of opioid induced sedation as measured by the Pasero Opioid-induced Sedation Scale (POSS) daily for the first 7 days then at week 6
7. The level of post operative nausea and vomiting (PONV) as assessed by the PONV impact scale daily for the first 7 days
8. Phantom limb or neuropathic pain as assessed by the S-LANNS daily for the first 7 days then at week 6 and 1 year

Completion date
01/05/2023

Eligibility

Key inclusion criteria
1. Patients aged 18 or over
2. Patients undergoing a primary above or below knee amputation for the symptoms resulting from peripheral vascular disease or diabetes
3. Patients undergoing amputation under general anaesthesia
4. Patients able to consent to amputation and study participation
5. Patients able to participate in assessing their pain using a Visual Analogue Scale

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Key exclusion criteria
1. Patients undergoing amputation for malignancy or trauma
2. Through-knee amputation
3. Other guillotine amputations
4. NCEPOD immediate eg:, undergoing amputation for uncontrollable infection/overwhelming infection, immediately life threatening limb ischaemia.
5. Unwillingness/ inability to comply with the requirements for follow-up visits
6. Known allergy or contraindication to receive any constituents of the study anaesthesia
7. Pregnant/lactating women
8. Patients undergoing more proximal or revision amputations on the ipsilateral side
9. Patients with a prior analgesia regime which includes a buprenorphine patch

Date of first enrolment
12/07/2021

Date of final enrolment
30/09/2022

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Freeman Hospital
Newcastle Upon Tyne Hospital Trust
Freeman Road
High Heaton
Newcastle
United Kingdom
NE7 7DN

Sponsor information

Organisation
Newcastle upon Tyne Hospitals NHS Foundation Trust

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Research organisation

Funder Name
Royal College of Surgeons of Edinburgh

Alternative Name(s)
The Royal College of Surgeons of Edinburgh, RCSEd

Funding Body Type
Private sector organisation

Funding Body Subtype
Associations and societies (private and public)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The current data sharing plans for this study are unknown and will be 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	version v1.5	11/03/2021	21/07/2021	No	Yes