Cooled Radiofrequency Ablation for the Treatment of Refractory Phantom and Residual Limb Pain; a Pilot Study.

Protocol Summary

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Background and Introduction

Introduction

Residual limb (RLP) and phantom limb pain (PLP) affects most amputees at some point in their life[1]. The incidence of PLP has been estimated to range between 50 – 80% [2-8]. RLP prevalence has been estimated to be 43%[9]. The peak of onset is bimodal and often appears within the first month and second year after amputation[10]. RLP is more common in the first year after amputation, with PLP becoming the predominate amputee pain complaint after one-year post-amputation[10].

Both RLP and PLP fall under the umbrella term "post-amputation pain." While these conditions are frequently found in combination, their clinical features and underlying causes are distinct [911]. PLP is a painful sensation in the distribution of the missing limb. Following amputation, abnormalities at multiple levels of the neural axis have been implicated in the development of PLP; changes include cortical reorganization, reduced inhibitory processes at the spinal cord, synaptic response changes and hyperexcitability at the dorsal root ganglion, and retrograde peripheral nerves shrinkage[12-14].

Residual limb pain has been called "neuroma pain" and is mechanistically distinct from PLP[11]. Neuromas may form as early 6-10 weeks after nerve transection, and are thought the produce ectopic neural discharges resulting in severe pain [15,16]. Evidence suggests RLP and PLP commonly co-occur and patients may struggle to differentiate between these pain types[17]. Risk factors include female sex, upper extremity amputation, pre-amputation pain, residual pain in contralateral limb, and time since amputation [10,18].

Depression, anxiety, and stress are known to exacerbate PLP / RLP[19]. Patients experiencing PLP and RLP also experience a higher incidence of indecisiveness, suicidal ideation, and thoughts of self-harm[8]. Current guidelines for treatment of PLP and RLP are not standardized. Treatments includes pre-operative analgesia, neuromodulation mirror therapy [13,20-22], imagery [20,22], acupuncture, transcranial stimulation [23], deep brain stimulation [35], and medications (including, but not limited to: TCAs [24-26], SSRIs [24], gabapentinoids [24,27,28], sodium channel blockers[25], ketamine[24], opioids [25], and NSAIDs[5]). Many agents have been injected in neuromas. These include local anesthetic [29], phenol[30], alcohol[31], and botulinum toxin [29]. These oral, intravenous, and nonpharmacological modalities have demonstrated limited success in the treatment of PLP / RLP. Neuroma cryoablation has been used, but this method of neural destruction poses technical challenges related to cumbersome needle placement and the requirement for time-intensive freeze-thaw cyclesl[32].

Conventional RFA has been studied on RLP [33,34]. Zhang et. al treated 13 patients with painful stump neuromas. The study started with alcohol neurolysis before using ultrasound-guided RFA for refractory cases. The frequency of sharp pain was reduced in all RFA-treated patients.

Kim et. al described a case in which ultrasound-guided RFA was successfully used to treat a sciatic neuroma of an above-knee amputee.

No outcome literature on the effectiveness of C-RFA technology has been published. C-RFA is similar in mechanism to conventional RFA: a thermal lesion is created by applying radiofrequency energy through an electrode placed at a target structure. In C-RFA, a constant flow of ambient water is circulated through the electrode via a peristaltic pump, maintaining a lowered tissue temperature by creating a heat sink. By removing heat from tissues immediately adjacent to the electrode tip, a lower lesioning temperature is maintained, resulting in less tissue charring adjacent to the electrode, less tissue impedance and more efficient heating of target tissue[35,36]. The volume of tissue heated, and the resultant thermal lesion size is substantially larger with C-RFA[37], conferring an advantage over conventional RFA[38]. Further, given the spherical geometry and forward projection the C-RFA lesions beyond the distal end of the electrode, the RFA probe can be positioned at a range of possible angles and still capture the target neural structure, whereas more fastidious, parallel positioning is required with conventional RFA[39]. These technical advantages increase the probability of successful denervation of neural pain generators that have variability in anatomic location. Additionally, a longer lesion of the RLP-generating nerve may be more reliably achieved with C-RFA compared to conventional RFA.

As such, the present study aims to define the attributable effect of cooled RFA on pain, physical function, and health-related quality of life in patients with post-amputation neuroma-associated residual limb pain. This prospective single-arm pilot study is intended to inform a future properly powered randomized controlled trial.

Purpose and Objectives

Objectives:

To assess changes in pain, physical function, and health-related quality of life in patients with post-amputation neuroma-associated residual limb pain after cooled radiofrequency ablation.

Study Population

Age of Participants: >18 years old on the day of enrollment

Sample Size:

At Utah:	20
All Centers:	10

Inclusion Criteria:

Inclusion Criteria:

1. Age greater than 18 years of age at day of enrollment.
2. Clinical diagnosis lower extremity amputation performed more than 1 year since study enrollment.
3. .
4. Pain duration of more than 6 months despite a trial of conservative therapy (medications, physical therapy) for 2 months.
5. Ultrasound and / or MRI imaging pathology consistent with clinical symptoms and signs.
6. Greater than 50% pain relief with a diagnostic neuroma block

Exclusion Criteria:

Exclusion criteria:

1. Refusal or inability to participate, provide consent, or provide follow-up information for the 12-month duration of the study.
2. Contraindications to diagnostic block or treatment ablation (active infection, bleeding disorders, and pregnancy or breastfeeding, active immunosuppression, participation in another phantom or residual limb pain trial within the last 30 days)
3. Non-neurogenic source of residual or phantom limb pain.
4. Active moderate to severe lumbar radiculopathy.
5. Any injection in the residual limb within the last 30 days.
6. Severe uncontrolled medical condition as determined by treating physician.
7. Severe psychological illness.
8. History of Inflammatory arthritis.
9. Malignancy within past 5 years except basal cell or squamous cell skin cancer.
10. Current opioid use exceeding 50 morphine milligram equivalents per day.
11. A history of alcohol or drug abuse within past 5 years.
12. Use of any investigational drug within past 30 days.
13. Pending litigation involving participant's residual limb pain.
14. Incarceration

Design

Prospective Biomedical Intervention or Experiment

Study Procedures

Recruitment/Participant Identification Process:

In-PERSON CONTACT: Participants will be recruited from the practices of the Principle Investigator and the Co-Investigators, the clinics of the University of Utah Orthopaedic Center, University of Utah Farmington Clinic, and the University of Utah South Jordan Health Center, and other University of Utah Hospital and Clinic locations. If the participant appears to be a candidate, he or she will be invited to participate.

WRITTEN OR ELECTRONIC CHART REVIEW will also be used to identify potential study participants on the PI and Co-PIs clinical and procedure schedules. The PI, Co-PIs, Clinical Research Coordinator, and Study Coordinator will perform the chart review to determine eligibility.

REFERRALS: Additional recruitment from University of Utah Hospitals and Clinics and local prosthetic offices. Flyers will be posted and information readily available for primary care providers to refer to the PM&R spine clinic. Flyers will be posted in waiting rooms, and clinic bulletin boards.

Participants will be personally invited to participate by either the PI or the Co-PI's either in person while in their respective clinics.

Informed Consent:

Description of location(s) where consent will be obtained:

Consent will be obtained at one of these University of Utah clinic locations: University of Utah Orthopaedic Center University of Utah South Jordan Health Center University of Utah Farmington Health Center

Description of the consent process(es), including the timing of consent:

As participants are identified by the PI or CO-I's as being possible candidates for this study they will invited to participate. It is anticipated that most subjects in this study will be identified mainly through the regular flow of the University of Utah clinics. The informed Consent process will occur either at the time the subject is in clinic or the participant may elect to complete the process at a later time. The patient will be greeted by the investigator or one of the study staff team members while in clinic. Patients will be given an IRB approved informed consent. All elements of the consent will be discussed with the participant, asking questions to assure they understand what is being asked of them. The patient will be allowed as much time as needed to consider fully if they would like to participate in the study. The patient will be encouraged to ask questions and if necessary take the consent home to discuss with family members and or other health care providers. The subject will be given sufficient time needed to review, ask and have his or her questions answered for a full understanding of the study and the procedures along with the risks and benefits. When the participant’s questions have been fully answered, we will have the patient sign consent prior to their planned procedure. Participants will be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Procedures:

Screening Visit: As participants are identified by the PI or CO-I's as being possible candidates for this study they will invited to participate. Main inclusion requirement, as listed in inclusion criteria, is that the patient is being scheduled for residual limb neuroma radiofrequency ablation (RFA) procedure as standard of care. If patient states interest in the study and wishes to discuss in more detail a research coordinator will discuss at time of appointment or call and answer any questions at a time convenient to the patient. If patient is interested, and does meet inclusion/exclusion criteria, and does not have time to do the baseline questions at time of appointment a qualified research staff member will call the patient to complete by phone. It is anticipated that most subjects in this study will be identified mainly through the regular flow of the University of Utah clinics. The informed Consent process will occur either at the time the subject is in clinic or the participant may elect to complete the process at a later time. Eligibility is determined by the inclusion and exclusion criteria. Qualifying volunteers will be asked to provide both written and verbal informed consent once a standard of care treatment plan has been agreed upon by the patient and treating physician.

Baseline: Participants who meet inclusion and exclusion criteria will be enrolled into the study after consenting to participate and before receiving residual limb neuroma RFA. This procedure is considered standard of care and are typically based on physician preference. Baseline data will be collected within 2 weeks prior to the scheduled procedure, this will include information from their examination and baseline questionnaires which include the following:

An electronic data collection system (REDCap via computer) will be used to record all pre-procedure and follow-up data as listed above (See attached PDF for baseline survey)

1. Age (years).
2. Sex
3. Height (cm).
4. Weight (Kg).
5. Duration of pain (weeks).
6. Date of amputation
7. Etiology of amputation
8. Level of amputation
9. Radiologic diagnosis based on ultrasound of residual limb.
10. Patient-Reported Outcomes Measurement Information System (PROMIS) 10
11. Analgesic medication log: dose and frequency of each medication
12. Brief Pain Inventory (BPI) with modification to include numerical rating scale (NRS) score (worst, least, average, current).
13. Gronningen Activity Restriction Scale (GARS)
14. Pinprick Sensory Threshold (Von Frey Hair testing at the neuroma site)
15. Pressure Pain Threshold (algometer testing at the neuroma site)

Additional questions for post procedure survey

16. Patient Global Impression of Change (PGIC)

    Patient satisfaction score (five-point Likert scale: 1, very dissatisfied; 2, dissatisfied; 3, neither satisfied nor dissatisfied; 4, satisfied; and 5, very satisfied)

Immediately after ablation the following will be obtained:

17. Post-injection Numeric Rating Scale (NRS) pain score

18. Adverse events, if they occurred

Questionnaires will be administered and collected from the participant through the University of Utah approved survey system of REDCap.

SOC Cooled Radiofrequency ablation (C-RFA) of Residual Limb Neuroma Procedure:

C-RFA:
Our RFA procedures will be performed similar to methods described by Zhang et. al[8] and Kim et. al[33] with modification accounting for appropriate C-RFA technique. This technique is currently standard clinical practice at University of Utah outpatient clinic sites. During the C-RFA procedure, the participant will be positioned prone. The participant's skin will be prepared with chloroprep. An ultrasound probe will be placed on the participants' residual limb at a transverse angle in order to view the nerve and associated neuroma in long-axis. The probe will be advanced to the site of the stump neuroma. An 18-gauge C-RFA electrode with a 4mm active tip (Coolief® Cooled Radiofrequency Kit, Avanos Health Inc, Alpharetta, GA) will be placed adjacent to the neuroma. This needle will be connected via wire to a cooled radiofrequency generator. Motor testing will be performed (2.0 V, 2Hz). Sensory testing will be performed (1.0 V, 50Hz) to reproduce or exacerbate the RLP and / or PLP. At the site of the neuroma, 2 mL of local anesthetic will be injected through the needle (without triamcinolone as used per Zhang[34]study). When the local anesthetic demonstrates pain relief, the needle will be placed into the nerve. C-RFA lesions will be created by using the typical C-RFA protocol with lesions performed for 165 seconds, with the RFA generator temperature set to 60°C (intralesional temperature >80 degrees)[42]. Once the procedure is completed, the needle will be removed. Following ablation, 0.5 mL of 0.5% bupivacaine will be injected at the site of the ablated neuroma to provide post procedure analgesia. No corticosteroids will be injected.

Following the Standard Treatment Procedure visit, routine scheduled follow-up will occur at 1 month (+/- 1 week), 3 months (+/- 2 weeks), 6 months (+/- 2 weeks), and 12 months (+/- 2 weeks) at which times all follow-up measures will be obtained. These questions will be administered over the phone or be sent to you using a secure REDCap survey by email. If received by email it will be in the form of two e-mail links in which you will again be asked questions regarding your pain level, changes in activity limitations, symptoms, emotions and

overall quality of life related to your painful condition and to record current use of opioid and non-opioid analgesic use. This part of the survey should take 10 minutes.

This study is intended to monitor outcomes for 12 months following C-RFA of residual limb neuroma.

Procedures performed for research purposes only:

1. survey/questionnaire

Statistical Methods, Data Analysis and Interpretation

Data Analysis Plan

A categorical responder analysis will also be performed using >50% pain relief in PLP and RLP, as well as the minimally clinically important change (MCIC) for secondary outcome measures for which an MCIC has been defined, and >30% improvement for secondary outcome measures for which an MCIC has not yet been defined.

While there is no standard residual limb pain outcome recommendation, the NIH's recommendation on pain interventions was applied to this study. These secondary outcomes include PGIC score less than 3 (indicating "improved" or "very much improved"), a 6.8 or greater point reduction on the MQS III score (equivalent to approximately 10 daily morphine equivalents).

Statistical analysis

Means and standard deviations of participant demographic data, as well as pain, functional, and other outcome data will be calculated. Proportions and 95% confidence intervals will be calculated for categorical data.