A Prospective, Randomized Trial of Liposomal Bupivacaine Compared to Continuous Nerve Catheters on Pain Control and Post-Operative Opioid Use in Receiving Popliteal Nerve Blocks for Below the Knee Amputation

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INTRODUCTION

Lower extremity amputation is a common surgical procedure often due to limb ischemia or complications related to diabetes mellitus. Managing postoperative pain can be quite challenging in this patient population and persistent post-surgical pain is not uncommon.[1] Peripheral nerve catheters (PNCs) that deliver a continuous infusion of local anesthetic have been shown to provide analgesic benefit dependent upon infusion duration and in the absence of catheter malfunction.[2-4] Unfortunately, PNCs can be difficult to place and rates of dislodgement are estimated at 30%.[5] Liposomal bupivacaine is an extended-release version of bupivacaine that allows for the gradual release of bupivacaine from liposomes. It is reported that single shot infiltration of liposomal bupivacaine has the potential of reducing pain for up to 72 hours, significantly longer than conventional bupivacaine that has a duration of action of 12-18 hours following infiltration.[6] As such, nerve blocks using liposomal bupivacaine for lower limb amputation could potentially afford improved pain relief comparative to PNCs, given the ease of single shot delivery, obviating the need for catheter placement.[7] Unfortunately,

there is conflicting evidence regarding the overall clinical efficacy of liposomal bupivacaine. Some studies have shown clear benefit over conventional bupivacaine,[8-10] while others have shown no difference in postoperative pain metrics following perineural injection.[11] To date, no study has investigated the effects of liposomal bupivacaine compared to PNCs for post-surgical pain control. In this pilot study, we intend to compare pain scores, opioid consumption, and length of stay in patients randomized to both treatment strategies. We also intend to conduct an exploratory analysis investigating incidence of phantom limb pain one month following surgery. Our results will inform the design of a larger powered study to investigate treatment effects.

BACKGROUND

Chronic pain following amputation significantly affects a patient's quality of life.[12] Phantom limb pain and stump pain are experienced by many patients following amputation, and about 70% of patients report phantom pain following a lower extremity amputation for peripheral vascular disease.[13] It has been suggested that phantom pain results from cortical reorganization following reduction of afferent nerve impulses and the extent of cortical reorganization appears to be proportionally related to the magnitude of phantom limb pain.[14,15] Also, it has been suggested that successful peripheral local anesthetic nerve blocks that relieve phantom pain reverse cortical reorganization, but not in patients whose nerve block was not successful in relieving the phantom pain.[3] To prevent the development of chronic phantom pain post amputation, different treatments have been reported in literature including the preemptive analgesic therapy.[14,15] The concept of preemptive analgesia as reported in several studies, includes the administration of epidural analgesia up to 3 days before the limb

amputation procedure and continued postoperatively.[16-20] In one study, the preemptive epidural group was compared to postoperative systemic opioid analgesia group.[17] In a different report, preoperative epidurals with bupivacaine and morphine were started 3 days prior to amputation and continued for 3 days after the procedure were compared to postoperative epidural analgesia for 3 days after surgery.[16] These studies reported significant lower incidence of phantom limb pain in the preemptive epidural analgesia groups.[16,17] However, the methodology in these studies was not clear because of limited information on the randomization, blinding, and pain assessment process. Also, other studies did not find any significant reduction in phantom limb pain with preemptive epidural analgesia.[19,20]

With no clear data on the impact of preemptive epidural analgesic therapy, investigators used perineural local anesthetic blocks in preventing phantom limb pain in patients undergoing amputation, with mixed results. One meta-analysis on the efficacy of perineural local anesthetic catheters after lower limb amputation showed about 50% reduction in postoperative opioid consumption in patients with PNC compared to placebo but PNC treatment did not affect postoperative pain scores, phantom limb pain, stump pain, or in-hospital mortality.[21] An observational study on a prolonged continuous PNC infusion of 0.5% ropivacaine in patients who underwent lower extremity amputation resulted in effective treatment of phantom limb pains and sensations.[3] However, PNC treatment has many limitations such as difficult placement, local intolerance of catheter, and accidental dislodgement. In contrast, a single shot regional nerve block using liposomal bupivacaine is easy to perform and can give up to 72 hours of pain relief, eliminating the need for PNC. Therefore, in this study, our goal is to assess if there is

any significant difference in pain score and opioid consumption between PNC treatment and liposomal bupivacaine in patients undergoing amputation.

Hypothesis

As a feasibility study, our primary outcomes were designed to assess the effectiveness of patient recruitment, retention and our proposed outcome assessments. We aim to obtain preliminary data investigating the effectiveness of perineural catheters and liposomal bupivacaine for the management of post-limb amputation pain. We will use the data that we collect to inform the design of a larger, appropriately powered study.

Specific Aims

Feasibility Aims

Aim 1: To determine the proportion of eligible patients seen at Maine Medical Partners Vascular Surgery Center that are successfully recruited for this study. We will assess the following outcome metrics:

- Overall time needed to recruit our goal of 30 total patients
- Effectiveness of our trial processes, including study implementation, subject retention and data collection strategy.

Aim 2: To obtain a sample size calculation for future study based on our effect size estimates

Intervention Effectiveness Outcomes

Aim 3: To compare the efficacy of the two treatment arms on analgesic and clinical outcomes following lower limb amputation. We will assess efficacy using the following

outcome metrics:

- Pain level measured using a numeric rating scale (NRS) of 0 to 10 during the first 72 hours after surgery
- Postoperative opioid consumption measured as morphine milligram equivalents (MME) during the first 72 hours after surgery
- Length of postoperative stay following surgical stop time

Aim 4: To compare the incidence of phantom limb pain 1 month after surgery. We will use mixed model regression or repeated measures ANOVA, as appropriate, to compare opioid consumption and pain scores over time between the two treatment arms. We will compare length of stay between the two groups using t tests or their nonparametric equivalents as appropriate; we will adjust for covariates using analysis of covariance.

SIGNIFICANCE

This study is significant because it will be the first prospective trial examining the analgesic efficacy of liposomal bupivacaine use for lower extremity limb amputation. Liposomal bupivacaine for limb amputation is within the scope of allowable treatment since our institution's Pharmacy and Therapeutics committee has given full approval for the unrestricted use of liposomal bupivacaine by an anesthesiologist for nerve blocks that we feel would benefit the patient. However, liposomal bupivacaine use for limb amputation is not current standard practice, and the majority of patients receive peripheral nerve catheters for this surgery. There are select instances where patients that cannot receive a nerve catheter (for instance, due to coagulopathy) are offered and provided liposomal bupivacaine for limb amputation analgesia. However, since no study has formally investigated liposomal bupivacaine for this purpose, we do not routinely

provide this service, as it is unclear if it is effective. Since efficacy has not been established, if a patient were to ask for a single shot liposomal bupivacaine block, we would not be able to provide one, unless there was contraindication to catheter placement. Additionally, liposomal bupivacaine is FDA approved for local anesthetic infiltration. Currently, at our institution, liposomal bupivacaine is routinely used for targeted peripheral nerve blocks for shoulder, knee and abdominal surgeries performed by anesthesiologists.

Lower extremity limb amputation has a high incidence of postsurgical pain, including stump pain and phantom limb pain.[3] Identifying optimal strategies to decrease acute pain is crucial for improving the incidence of chronic post-surgical pain. Although continuous nerve blocks using conventional bupivacaine can provide extended pain relief, there are many factors which can impair PNC efficacy. For instance, catheter placement can be quite challenging which can lead to block failure. Also, catheters can become dislodged, leak at the insertion site, and commonly get disconnected from the local anesthetic infusion pump, leading to interruption of analgesia. Since PNCs are an inserted foreign body, they carry a risk of infection greater than single shot local anesthetic techniques. The level of nursing care that is required to change infusion bags and troubleshoot pump problems is also higher with the PNC technique comparative to a single shot nerve block. Identifying an easy, reliable approach to provide multi-day pain relief will benefit patient care as well as current procedural and postoperative care workflows.

Phantom limb pain has high morbidity and with significant interference in quality-of-life, post-amputation. If our exploratory analysis reveals that liposomal bupivacaine can prevent the incidence of phantom limb pain or decrease the incidence of chronic pain,

this can have a profound impact on future post-amputation pain management.

This study is intended as an initial assessment of the utility of liposomal bupivacaine for postoperative pain management following lower limb amputation. Our hope is that this novel application of liposomal bupivacaine will inform the design of a larger, more robust prospective study on the effect of this intervention in this patient population.

STUDY DESIGN AND RESEARCH PROCEDURES

This is a prospective, randomized, unblinded clinical trial comparing liposomal bupivacaine with standard of care continuous local anesthetic infusions among patients scheduled for below the limb amputation.

Inclusion criteria: (1) aged 18 years or older who have the capacity to provide informed consent, (2) ASA class I-IV (3) primary amputation (4) English speaking

Exclusion criteria: (1) Patients unable to cooperate or consent to the study (2) allergy to local anesthetics (3) infection at needle insertion site (4) BMI > 40 kg/m2 (5) history of coagulopathy (6) emergency amputation (7) contralateral amputation (8) patients with substance use disorder diagnosis (9) on opioids with MME greater than 90 MME/day (10) patients on buprenorphine or methadone

Subject Selection

Inclusion of women and minorities. We will not exclude any adults on the basis of age, gender, or ethnicity and our projected enrollment is based on most recent Maine census.

Inclusion of individuals across the lifespan. We will exclude individuals under the age of 18 years from enrollment in this trial. These patients require personalized treatment strategies often coordinated by multiple providers therefore we will not alter these

treatments decisions for study purposes.

Source of subjects and recruitment and methods:

Study participants will be recruited from inpatient and outpatient settings. Outpatient participants will be informed of the study during their preoperative surgical visit at the Maine Medical Partners Vascular Surgery Center as well as at the Pre-amputation Consultation Rehabilitation Clinic. Registered nurses and providing physicians will be briefed on the objectives of the study and inclusion/exclusion criteria. These providers will introduce the study to patients that appear to meet inclusion criteria to determine baseline interest and to provide the patient with contact information for the study team.

In addition to being introduced to the study directly by study staff, flyers describing the study will be posted in the clinics and visible to patients. Contact information, including study staff phone number, will be listed on the flyer for patients to contact if they are interested in enrollment. If a patient reaches out after seeing the flyer, a member of the study team will tell them more about the study over the phone (script included in IRB submission) and will send the consent form, either by mail or via DocuSign, for the patient to review. The patient will be given contact information to reach out to study staff with questions after receiving the consent form.

DocuSign Process:

1. A DocuSign link for an electronic consent is sent to the subject's email address
2. Research staff contact the subject by telephone or videophone to have the informed consent conversation. *This step confirms subject identity.*

3. The information for the informed consent discussion will be made using the IRB-approved consent form which is written in a language comprehensible to the potential participant. The information presented in the consent form and by the research staff will detail the nature of the trial and what is expected of participants, including any potential risks or benefits of taking part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.
4. After allowing the potential participant time to read the informed consent document; research staff will answer any additional questions.
5. If the patient agrees, a complete electronically signed and dated copy of the consent will be provided to subject via Docusign.
    a. A complete electronically signed and dated copy will be printed and scanned into subject's electronic medical record
    b. A complete electronically signed and dated copy will be kept with study records.

We will use Docusign to obtain consent electronically for patients able to complete that process. If the patient opts to participate in the study and does not utilize Docusign, the consent form will be reviewed with participants over the phone. Patients who do not wish to use DocuSign but wish to participate will have the opportunity to sign the consent form when they present for surgery (prior to receiving any anxiolytics or other medications that might interfere with their ability to provide consent).

For inpatient recruitment, patients that are admitted to the hospital will be identified using the Maine Medical Center operating room schedule. Study staff will identify patients at least two days prior to their surgery to introduce them to the study and answer any questions. Informed consent forms for inpatients will be presented by study staff and signed by subjects in person per standard processes.

Participants will be reminded that their involvement in the study is completely voluntary and that they can choose to withdraw from the study at any point. They will also be advised that withdrawing from the study would not affect the care they receive at MMC and that any data collected prior to withdrawal from the study will be retained for data analysis. Participants will be reimbursed $40 for completing the one-month assessment in the form of a gift card.

On the day of surgery their anesthesiologist will also elicit and answer any questions or concerns regarding the study for the purposes of ongoing consent. Patients will be informed of the potential risks and complications of nerve block placement that are inherent to their scheduled anesthetic and independent of their participation in the study, per standard clinical practice. These include bleeding, infection, and nerve injury.

STUDY PROTOCOL

Randomization

After informed consent is obtained, patients will be randomized into the two study groups in a 1:1 ratio as follows:

- Group A- Single shot perineural popliteal nerve block injection of 20cc 13.3% liposomal bupivacaine combined with 20cc 0.50% bupivacaine hydrochloride within one hour prior to surgery. Saphenous single shot nerve block of 20cc 0.25% bupivacaine. (Intervention arm)

- Group B- Placement of continuous perineural popliteal nerve block catheter with injection of 20cc 0.5% bupivacaine within one hour prior to surgery, followed by continuous infusion of 8cc 0.3% ropivacaine (current standard practice) for at least 72 hours following surgery. Saphenous single shot nerve block of 20cc 0.25% bupivacaine. (Control Arm)

The randomization scheme will be developed using NQuery Software (Statistical Solutions, Boston, MA). The analyst will provide the research coordinator with randomization assignments in sequentially-numbered opaque envelopes. As the study is unblinded, both patients and providers will be aware of the randomization assignment. To help mitigate bias, the team members collecting and entering data will be masked regarding the patient's assignment. The REDCap database has the randomization assignments in an instrument separate from the study data collection instruments, allowing for data entry without seeing which group the subject is in.

The ultrasound guided nerve blocks will be performed by experienced members of the regional anesthesia team. Patients will be placed on standard ASA monitors and given supplemental O2 via nasal cannula or simple mask. The injection site(s) will be prepped and draped using standard infection control and sterile protocols. Light sedation will be given as needed by the attending anesthesiologist, and skin infiltration of the puncture site with 2% lidocaine will be performed.

An ultrasound will be used to visualize the popliteal nerve and any relevant structures. After the targeted nerve structures have been identified, the peripheral nerve block needle will be advanced under direct ultrasound visualization. There is a risk of the study drug being injected into a blood vessel; however, the risk is reduced since the provider will be using an ultrasound to guide needle placement. An additional safety measure to prevent injection into a blood vessel is that the provider will confirm proper placement by checking for a negative aspiration of blood and air before depositing the study drug in the immediate vicinity of the popliteal nerve using low pressure injections. The safety measures in place to prevent injecting the drug into a blood vessel during nerve blocks are effective, in the past 10 years at MMC there has not been a single case of local anesthetic injection into a blood vessel while using ultrasound guidance for peripheral nerve block placement leading to local anesthetic systemic toxicity. Additionally, all nerve blocks will be performed by senior faculty on the acute pain management service, as opposed to residents or trainees, further making this risk extremely rare.

In the event of poorly controlled pain at any point during the study, we will provide the patient with appropriate analgesic rescue agents to ensure that post-surgical pain is adequately controlled. All pain medications will be documented for subsequent analysis.

Outcome data will be collected by a blinded member of the anesthesia research team as outlined in the data collection table. Vital signs, NRS pain scores, and adverse symptoms will be recorded in the subject's medical record as standard practice. This information will be collected for study purposes.

The local anesthetic infusion will be run continuously for at least 72 hours in the PNC group. We chose not to infuse a continuous saline solution in the intervention group

because we wanted to avoid dilution of the liposomal bupivacaine solution which could potentially impair its efficacy. We also did not want to expose patients to the unnecessary risk of catheter infection. If a catheter leaks, becomes dislodged, or malfunctions prior to the 72 hour time period, the local anesthetic infusion will be discontinued and the time of discontinuation will be recorded for subsequent comparative analysis. Similarly, if a participant decides to withdraw from the study prior to the 72 hour time point, data collected prior to withdrawal will be included in the study unless the subject requests that their data be removed from the study database.

For multimodal pain control, all patients will receive the following:

Acetaminophen 650mg PO every 8 hours standing

Ketorolac 30mg IV every 6 hours for 4 doses followed by ibuprofen 600mg PO every 6 hours

Gabapentin as needed for neuropathic pain control.

If a participant has an allergy or aversion to any of these medications, they will not receive the medication. This will be documented in REDCap and will not influence participation in the study.

In the event of poorly controlled pain in either group- including block or nerve catheter failure – opioid medications will be given IV or PO as second line analgesic agents for pain control. Opioid consumption will also be recorded in REDCap.

One month following surgery, patients will be contacted via telephone and will be asked questions regarding residual pain, opioid consumption, and phantom limb sensations or pain. Patients will be asked to report pain using the numeric rating scale used at the 0-72

hour timepoints in addition to the short form McGill Pain Questionnaire-2 that has been used extensively in published studies to rate pain quality and intensity, including questions regarding neuropathic pain.[22] They will also be asked two questions about phantom and residual limb pain from the Trinity Amputation and Prosthesis Experience Scales-Revised (TAPES-R).[23] The phone call will last for 30 minutes and patients will be reimbursed $40 for this phone call.

Data Collection

The data we propose to collect are summarized in the attached Data Collection document. The data will be collected from the patient's EPIC electronic medical record. We will collect data on intraoperative opioid consumption, type of anesthesia, total PACU opioid consumption-normalized for time spent in PACU, and 24, 48, 72-hour opioid consumption. All opioid consumption will be converted into MME.

Measures for Aim 1 and 3 (Pain scores)

The primary outcome of this study will be composite pain scores 24 hours after surgery. Others have shown that composite pain scores quantify pain with greater accuracy than a single measurement. Jensen et. al. concluded in their study that composite pain intensity scores from two or more individual ratings of pain are valid for detecting treatment effects.[24] Pain scores will be measured using a numeric rating scale (NRS) (0=no pain; 10= worst possible pain) "Worst," "average," and "least" pain scores will be assessed for the preceding time interval at 24, 48, and 72 hours following surgery. Inpatient pain scores will be collected every 6 hours per an order set connected to the study. To collect pain scores, nursing staff asks patients to rate their current pain on a

scale from 0-10. If a participant is discharged prior to 72 hours after surgery, study staff will provide patients with a log to keep a record of their pain scores every 6 hours, in order to mitigate recall bias in anticipation of being contacted by research staff. Study staff will call discharged patients and ask them to report their pain scores for each 24 hour period between discharge and 72 hours postoperatively as recorded on the forms they were given at time of discharge.

Measures for Aim 2 and 3 (Opioid consumption)

For our opioid consumption assessments, data will be collected intraoperatively, in the PACU and at the 24hr, 48hr, and 72hr timepoints following surgery, as is standard for surgical patients. Information on opioid type and dose will be obtained through review of the participant's electronic medical record or through phone assessment, depending on point of hospital discharge. Opioid amounts will be converted into MMEs.

Measures for Aim 4 (Postoperative length of stay)

The time of surgical stop time and discharge will be extracted from the medical record and calculated to length of stay in hours.

Measures for Aim 5 (Phantom limb and chronic pain)

To evaluate incidence of phantom limb pain, participants will be contacted via telephone and asked questions current pain and phantom limb sensations. Pain scores will be 0-10 using the same numeric rating scale used postoperatively. The short form McGill Pain Questionnaire will be used to evaluate pain quality and intensity. Questions from the Trinity Amputation and Prosthesis Experience Scales-Revised (TAPES-R) will address phantom and residual limb pain.

All phases of this study will comply with Health Insurance Portability and Accountability Act (HIPPA) regulations. Data will be collected and stored in a REDCap database to preserve privacy and confidentiality. Only members of the research team will have access to the data that participants have consented to provide. Participants will be informed that they have the right to not answer any question that makes them feel uncomfortable.

Data Analysis

Since this is a feasibility study, there currently is insufficient data to justify our sample size calculation. We will design our study as parallel group pilot trial with a with a total sample size of 24 patients, 12 patients per arm. This number has been previously described for maximal gain in precision around mean in studies with small sample sizes.[25] To help account for attrition at the one month follow up mark, we will increase the total enrollment to 30, with 15 patients per arm. The preliminary information we obtain will guide our power calculation for our future larger-scale trial. Based on our preliminary EPIC query, between 6/1/2019- 9/1/2020 there were 80 patients that underwent below the knee amputation at Maine Medical Center. We anticipate we would be able to recruit a sample of 15 patients per arm within 9-12 months of the study start date.

Adverse Events Documentation and Reporting

Since this study would not have additional risk or adverse events different than for patients not enrolled in the study and there are no additional risks associated with the use of liposomal bupivacaine, we will not have a DSMB. The study will be monitored for

safety and the PI will report any serious, related, and unanticipated adverse events (SAEs) and any unanticipated problems (UPs) to the MaineHealth IRB according to their requirements (SAEs within 5 business days and UP within 10 business days). Members of our study staff will be trained to monitor and review adverse events, which will first be reported to the PI, who will be responsible for advising the IRB.

Table 1: Major and Minor Adverse Events

	Item	Action	Regulatory Reporting
Major AE	1. ED admission due to severe pain 2. Intractable Pain	Alert acute pain service (APMS) for management recommendations	Within 5 days to IRB
Minor AE	1. Hospital discharge delay due to poor pain control 2. Pain worse than anticipated	Alert APMS team as needed	Within 10 days to IRB

Data Management and Storage

Data will be obtained from the patient medical record and will be collected in and stored securely in a web-based, HIPAA-compliant REDCap database. Only the project team will have password protected login access to the database. Data will be entered manually by members of the project team, who will enter data from EPIC directly into REDCap without requiring an interim or paper form.

To further safeguard patient information, we will create multiple instruments in REDCap, one with the patient name, MRN, Date of Birth (DOB) and the study ID (which will be referred to as the “Master List”), a second instrument with randomization assignments, and a third instrument that will be used to collect study data and will contain the study ID and not the patient name or MRN. Once all the data have been collected and verified, the Master List will be deleted and participants will thereafter be identified only by their unique project codes. All HIPAA-related documentation will be stored for a minimum of 6 years after study completion. The REDCap database will be deleted three years after final publication/presentation of the data.

Statistical Analysis

Data will be summarized using descriptive statistics. Categorical variables will be reported as frequency (n,%), and continuous variables will be reported as means with standard deviation or as median with range, as appropriate. Fisher’s exact test will be used to compare categorical data between study groups. T tests or Mann Whitney U test will be used, as appropriate to compare continuous data between study groups. Data will be analyzed using SPSS statistical software version 25 (IBM SPSS Inc, Armonk, NY).

Limitations

Since this is a randomized prospective trial, it will be harder to recruit for this study as compared to a retrospective study and this study will be limited by its initial small sample size. Due to the small sample size, we likely will not be able to match participants recruited for each group against variables such as BMI, HTN, smoking, and other conditions that are associated with chronic pain and increased opioid consumption. This limitation could introduce confounders in our study if a disproportionate number of subjects, by chance, are recruited into the intervention group compared to the control group, for instance. This study also is not a placebo-controlled trial because administering a saline infusion in the liposomal bupivacaine arm could potentially dilute the study drug and impair its efficacy. Neither is it blinded, which could introduce additional bias. However, we attempt to mitigate this by masking the data entry. The REDCap database has the randomization assignments in an instrument separate from the study data collection instruments, allowing for data entry without seeing which group the subject is in.

Despite all of these limitations, prospective placebo-controlled trials are the gold standard for clinical trials. We anticipate the benefits of this study design, where bias is mitigated and where many variables are controlled for, will outweigh the above limitations.

Study Timeline and Future Plan

We anticipate it will take 9-12 months to complete the subject recruitment for this trial. It will take one month to complete data analysis and one month to produce a manuscript for publication.

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