Liposomal Bupivacaine vs Peripheral Nerve Block

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Abstract:

Liposomal bupivacaine has gained interest in recent literature for its potential to be an effective adjunct to other pain control modalities in a multi-modal approach to post-operative pain control. Liposomal bupivacaine is an analgesic that is suspended in lipids to allow for gradual release of the analgesic over a 72-hour period (NAMDARI). From prior literature, the utilization of local analgesics infiltrated into surgical sites have been shown to reduce pain in the immediate post-operative period in foot and ankle surgery (GADEK). However, the evaluation of liposomal bupivacaine in foot and ankle surgery is limited. One prospective study found that the addition to liposomal bupivacaine to a multi-modal pain management protocol for forefoot surgery resulted in decreased pain scores during the first four post-operative days as well as fewer refills of opioid pain medication prescriptions, although both findings were not statically significant (ROBBINS). As the general medical community and public policy makers continue to focus on decreasing the amount of opioid pain medications prescribed and available in the community due to the opioid epidemic, liposomal bupivacaine has the potential to be a useful adjunct in the management of post-operative pain without reliance on opioid prescriptions. The goal of our investigation is to compare the efficacy of local administration of liposomal bupivacaine versus the efficacy of a peripheral nerve block in terms of post-operative pain scores after elective ankle and hindfoot surgery. We hypothesize that there will not be a significant difference in the pain scores of these two groups in opioid naïve patients. Furthermore, we aim to determine if there are differences in the amount of opioid medications utilized for post-operative pain control, patient satisfaction scores, functional outcomes, complications, and unscheduled healthcare contact between the two groups. In order to accomplish our goal and aims, we plan to conduct a randomized, controlled investigation.

Background and Significance:

Liposomal bupivacaine has gained interest in the orthopaedic community for its potential to be a useful adjunct in the control of post-operative pain. Especially with the recent focus on decreasing the number of opioids prescribed and available to the general public due to the opioid epidemic, liposomal bupivacaine is being investigated in numerous orthopaedic sub-specialties as a promising way to control post-operative pain, maintain high patient satisfaction, all the while decreasing dependence on opioids for pain control. The arthroplasty arena has led the way in the investigation of liposomal bupivacaine in the management of post-operative pain. Sabesan, et al. demonstrated excellent pain relief for patients undergoing shoulder arthroplasty who received a local liposomal bupivacaine injection in addition to a single-bolus interscalene block compared to patients who received continuous interscalene nerve block (SABESAN). Yu, et al. demonstrated that patients who received a local liposomal bupivacaine injection after total knee arthroplasty consumed slightly less morphine equivalents of opioids than patients who received a femoral nerve block (YU). Given these findings, the utilization of liposomal bupivacaine in foot and ankle surgery is of interest as well.

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The goal of our investigation is to compare the efficacy of local administration of liposomal bupivacaine versus the efficacy of a peripheral nerve block in terms of post-operative pain scores after elective ankle and hindfoot surgery. We hypothesize that there will not be a significant difference in the pain scores of these two groups in opioid naïve patients. Furthermore, we aim to determine if there are differences in the amount of opioid medications utilized for post-operative pain control, patient satisfaction scores, functional outcomes, complications, and unscheduled healthcare contact between the two groups. In order to accomplish our goal and aims, we plan to conduct a randomized, controlled investigation.

Hypothesis and Aims:

Hypothesis:

We hypothesize that there will not be a significant difference in the pain scores of patients randomized into the liposomal bupivacaine group and the peripheral nerve block group in opioid naïve patients.

Specific Aim 1:

To compare post-operative pain scores after elective ankle and hindfoot surgery in patients who receive a local infiltration of liposomal bupivacaine versus a peripheral nerve block.

Specific Aim 2:

To compare opioid consumption in morphine equivalents after elective ankle and hindfoot surgery in the two groups.

Specific Aim 3:

To compare patient satisfaction scores after elective ankle and hindfoot surgery in the two groups.

Specific Aim 4:

To compare functional outcomes after elective ankle and hindfoot surgery in the two groups.

Specific Aim 5:

To compare complication rates after elective ankle and hindfoot surgery in the two groups.

Specific Aim 6:

To compare rates of unscheduled healthcare contact after elective ankle and hindfoot surgery in the two groups.

Study Design:

This is a prospective, randomized trial to investigate whether there is a difference in pain score, opioid consumption, patient satisfaction, functional outcomes, complication rates, and unscheduled healthcare contact associated with local liposomal bupivacaine infiltration versus peripheral nerve block in patient undergoing elective ankle and hindfoot surgery. Approximately 50 patients will be randomized.

Study Population:

Approximate Number of Subjects:

Approximately 50 total Geisinger patients will participate in the study.

Inclusion Criteria:

1. Patients 18 years of age or older
2. Patients undergoing elective primary ankle or hindfoot surgery (ankle arthrodesis, subtalar arthrodesis, triple arthrodesis, total ankle arthroplasty, peroneal tendon debridement/transfer, Cavus Reconstruction, Medial Displacement Calcaneal Osteotomy, Dwyer Osteotomy)

Exclusion Criteria:

1. Patients who are undergoing revision surgical procedure
2. Patients who have taken opioid pain medications in the past 3 months prior to surgical procedure
3. Patients who have allergies to any of the medications or components of medications investigated in the study
4. Patients currently incarcerated
5. Patients who cannot read and speak English

Study Recruitment:

The study investigators will identify potential study participants in the outpatient clinic. The patients that meet inclusion criteria will be approached by the physician investigator, research coordinator(s), and/or research assistant(s) during their orthopaedic clinic visit and will be asked to participate in the study. After hearing the study explanation, if the patient is interested in participating, the physician investigators, research coordinator(s) and/or research assistant(s) will review, with the patient, the informed consent form asking authorization to access/use their PHI. The patient will sign and date the form after all questions have been satisfactorily answered by the study team. Recruitment materials will consist of the informed consent form.

Study Duration:

Approximate Duration of Subject Participation:

Patients will participate in the study for approximately 3 months – from initial recruitment to end of participation.

Approximate Duration of Study:

The study will be completed in approximately 12 months. The end of the study is the last visit of the last subject, or end of collection of data from the patient's electronic health record.

Procedures:

Patients who meet inclusion criteria will undergo a selection process, and if they choose to participate will be randomized into one of two groups. The randomization scheme will be created with the use of an internet based randomization website (https://www.randomizer.org). Qualifying subjects will be randomized into one of two groups prior to their surgery:

1. Liposomal Bupivacaine Group
    a. Pre-operative
        i. No peripheral nerve block will be given
    b. Intraoperative
        i. Local infiltration of 20cc of Liposomal Bupivacaine infiltrated to the surgical area
    c. Post-operative (At Discharge)
        i. Oxycodone 5mg every 6 hours as needed for pain (30 tablets)
        ii. Acetaminophen 500mg every 6 hours scheduled

2. Peripheral Nerve Block Group
    a. Preoperative
        i. Peripheral Nerve Block performed by anesthesia team (blocks will be given by same anesthesia provider utilizing same technique every time in order to reduce variations in delivery of peripheral nerve block).
    b. Intraoperative
        i. No local analgesic agent infiltration
    c. Post-operative (At Discharge)
        i. Oxycodone 5mg every 6 hours as needed for pain (30 tablets)
        ii. Acetaminophen 500mg every 6 hours scheduled

Patients will be randomized as to which analgesia regimen they will receive. The surgeon will not be blinded.

On the day that the patient is consented for the study, they will complete the following standard of care assessments in clinic:

1. VAS Pain Scale
2. Pain Catastrophizing Scale
3. PROMIS Self-Efficacy of Managing Symptoms

On the day of surgery, all qualifying patients will undergo their elective ankle or hindfoot surgery under standard practices. Randomized patients will receive pre-operative peripheral nerve block prior to the procedure. The participating surgeon will perform the procedure in accordance with their standard practice. Liposomal Bupivacaine will be injected prior to incision and after wound closure. Patients will

be placed in sterile dressings and a post-operative splint in accordance with the surgeon's standard practice. All patients will receive discharge instructions based on the surgeons standard practice. All patients will receive the same post-operative opioid pain regimen.

Patients will keep a pain journal, documenting their pain from postoperative days 1-7. It will include pain score as well as pain medication utilization documentation starting from immediately in the Post-Anesthesia Care Unit, 6 hours post-op, and 12 hours post-op. Afterwards, participants will be asked to document pain score and pain medication utilization daily from post-operative days 1-7. They will bring their pain journal with them to their first postoperative visit.

Patients will be seen at 2 weeks and 6 weeks postoperatively. During these visits, a routine wound check will be performed. The patient's range of motion and pain will be assessed. Any complications will be recorded. All postoperative care other than the medications prescribed at the time of discharge will be in accordance with each surgeon's standard practice. At each of these two visits, patients will complete the following assessments:

1. VAS Pain Scale
2. Pain Medication Utilization Questionnaire
3. Pain journal collection

At the conclusion of the 6-week post-operative period, the EMR will be reviewed an any instances of unscheduled healthcare contact (email, MyGeisinger messages, telephone calls, unscheduled clinic visits, ED visits) will be recorded and analyzed for cause.

All surgeons participating in the study will adhere to the randomization, treatment and follow-up protocol. There will be 2 participating sites within the Geisinger system (GMC and GMC Woodbine) whom will participate in this research project.

Study Time and Events Table

Study Procedures	Visit ~pre-surgery	Visit Day of Surgery	0, 6, & 12 Hours Post Op	Visit 2 week follow-up	Visit 6 week Follow-up
Office Visit	X			X	X
Prescreen	X				
Provide Info Sheet	X				
Review Inclusion/ Exclusion	X	X			
Demographics, medical history, habits, historical diagnoses	X				
Consent of Patient	X				
Randomization	X				
Outcome measures / examination assessment recorded	X		X	X	X
Analgesia administration		X			
Surgery		X			
AE / Complication Reporting		X	X	X	X

Primary Endpoints:

The primary endpoint is to determine if there is a statistically significant difference in pain scores (VAS Pain Scale) for patients undergoing elective ankle and hindfoot surgery randomized to a group receiving intra-operative liposomal bupivacaine infiltration versus a group receiving a peripheral nerve block.

Secondary Endpoints:

1. Differences in morphine equivalents consumed for post-operative pain control
2. Difference in patient satisfaction score
3. Differences in functional outcomes
4. Difference in complications
5. Differences in unscheduled healthcare contact

Statistics:

Statistical analysis will be performed by Les Kirchner

Data Management

Data to be Collected:

The following data will be collected from the EMR:

- PHI elements (will not be included in final dataset)
- Medical Record Number (MRN)
- Name
- Date of Birth
- Patient Demographics (Age, gender, weight, height, Body Mass Index (BMI))
- Medical History
- Narcotic use history
- Inflammatory or Rheumatoid Arthritis
- Complications / AE
- Wound Hematoma
- Superficial wound infection (defined as any prescription for post-op antibiotics)
- Wound complications
- Deep infection (defined as need for surgical irrigation and debridement)
- Crossover
- Number of patients randomized to liposomal bupivacaine group that request peripheral nerve block
- Unscheduled healthcare contact and reason for contact
- Phone calls
- Emails
- MyGeisinger Messages
- Unscheduled clinic visits
- ED visits
- Dates
- Date(s) and information related to of admission, surgery, and discharge
- Date(s) and information related to clinic visits

The following data will be collected during the patient clinic visits:

- VAS Pain Scale (0-10)
- Pain journal from post-operative days 0-7 including pain medication utilization and pain scores

Data Collection and Storage

The data points outlined above will be reviewed and collected from the EMR by the study coordinator(s), project coordinator(s) and/or co-investigators. A data request will be submitted to the BC Data Broker, an independent person from the study team.

A member of the IRB-approved Geisinger study team will perform a manual chart review for data points not captured during the BC data pull. A member of the IRB approved study team will randomly assign

study ID numbers in order to protect the identity of the subject. After the dataset has been de-identified, an IRB-approved study team member will forward the completed dataset to Les Kirchner for analysis. All study data will be kept in GHS maintained username/password-protected computer files and hard copy data will be double locked and accessible only to the study investigators in the locked office of the Study Coordinator. Only group-level information without personal identifiers will be included when presenting results or submitting manuscripts for publication.

Personal or sensitive information that could be potentially damaging to participants (e.g. relating to illegal behaviors, alcohol or drug use, sexual attitudes, mental health, etc.) will not be collected. With concerns to HIV/AIDS status, if the status is already in the participant's medical record it will be reported into the CRF as a "yes" or "no," otherwise it will be reported in the CRF as "not assessed." Regarding collected mental health information that could be potentially damaging to participants, participants indicating that they are very depressed, thus raising concern regarding their mental state, will be referred to their primary care physician.

No PHI will be shared outside of the IRB approved study staff.

Records Retention

Records of data generated in the course of the study will be kept indefinitely and may be used for future research purposes.

Adverse Event Reporting

Clinical adverse events (AEs) will be monitored throughout the study. All AEs will be reported to the institutional review board (IRB) according to IRB policy. The date and time of onset and outcome, course, intensity, action taken, and causality to study treatment will be assessed by the study PI.

Definitions

An adverse event (AE) is any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, or laboratory or physiologic observations occurring in a person given a test article or in a clinical study. The event does not need to be causally related to the test article or clinical study.

Adverse Events related to Elective Ankle and Hindfoot Surgery:

- Infection
- Wound healing issues
- Persistent pain
- Peripheral nerve injury
- Arterial injury
- Wound complications

A protocol-related adverse event is an AE occurring during a clinical study that is not related to the test article, but is considered by the investigator or the medical monitor (or designee) to be related to the research conditions, i.e., related to the fact that a subject is participating in the study. For example, a

protocol-related AE may be an untoward event occurring during a washout period or an event related to a medical procedure required by the protocol.

Recording and Reporting

A subject's AEs will be recorded and reported from the signing of the informed consent form to end of study period.

Protection of human subjects

Informed Consent

The investigator will provide for the protection of the subjects by following all applicable regulations. The informed consent form will be submitted to the IRB for review and approval. Prior to having any study procedures performed, the patient will be asked to read and then sign the informed consent form if they agree to participate in the study. The subject will receive a copy of the signed/dated informed consent form for their records. The original copy of the informed consent form will be scanned into the subject's EMR and the hardcopy will be filed in the subject's study binder. The rights and welfare of the subjects will not be affected. We are requesting to observe and record variables that are normally collected and entered into the patient's EMR in the course of standard clinical care. The purpose of recording data for this prospective study (in addition to the EMR) is simply to ensure that discrete, standardized format (since some variables, while stored in the EMR, may appear in physician notes as free text).

There is very little to no risk associated with this study. The risk to study participants is related to accidental disclosure of PHI (i.e. MRNs, dates). Any time information is collected for a study there is a small risk of breach confidentiality. However, this risk is not greater than the risk that already exists in clinical settings when handling medical data.

A partial waiver of HIPAA authorization is being requested for this study. A waiver is necessary for the research to be practically conducted because the research team much review the patient's PHI to determine eligibility. The research team would be unaware of potential eligible patients without reviewing that patient's relevant medical information. If the patient does not meet eligibility criteria, they will not be approached to partake in the study. While PHI is being requested, it is the minimal amount necessary to ensure patients are eligible based on the inclusion criteria.

Protection of Human Subjects Against Risks

The investigator will provide for the protection of the subjects by following all applicable regulations. Anticipated risks in this study are minimal. This study will not affect patient care or access to care. The major risk to human subjects in this study is the accidental disclosure of PHI. In this regard, the assignment of a coded test ID number to each individual participant and the protocol of providing only the necessary associated clinical information to the remainder of the research team mitigate this risk.

All study data will be kept in Geisinger Health System maintained username/password-protected computer files and hard copy data will be double locked and accessible only to the study investigators. Only group-level information without personal identifiers will be included when presenting results or submitting manuscripts for publication.

Publication Plan:

We plan to prepare and submit the results of this study for presentation at national meetings and in peer-reviewed journals.