Study Title: Pilot Study: Extended Regional Anesthesia to Prevent Chronic Pain After Ankle Fracture Surgery

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Research Team:

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Sponsor:

US Air Force 711th HPW (DOD)

1. **Length of time for research**
   a. data collection completion: 1 year 6 months
   b. data analysis and report writing/publication:6 months

2. **Research Location(s):** University of Cincinnati Medical Center (UCMC), Holmes Hospital (UCMC), West Chester Hospital and UC Medical Science Building/CARE Crawley

3. **Abstract/Brief Overview:**

Chronic pain affects over a third of adults in the United States. Trauma and surgery are common precipitating causes of some chronic pain conditions, and up to 81% of combat trauma survivors have chronic pain. For many patients current treatments are ineffective. Preclinical studies suggest that blocking peripheral nerve activity early after a precipitating injury, for 5 – 7 days, can prevent chronic pain development. This pilot study will test the hypothesis that prolonged regional peripheral nerve block will reduce development of chronic pain in patients undergoing surgery for ankle fracture. Regional nerve block using local anesthetics delivered by ambulatory pump is used in some types of surgeries but is not routine for ankle fracture patients in our hospitals. Patients will be randomized to standard care (single shot peripheral nerve block prior to surgery) or experimental (the same single shot nerve block, followed by continuous popliteal nerve block with ropivacaine starting just after surgery). The primary outcome will be scores on a validated ankle/foot pain questionnaire that includes questions on function. Subjects will be followed for one year. Secondary outcome will be postoperative opioid use.

4. **Purpose of Study:** (including specific aims and hypothesis)

   This is a pilot study that will begin to test the hypothesis that 5 day regional nerve block will reduce chronic pain after ankle fracture surgery. Specific Aims are:

   1. Enroll subjects undergoing ankle fracture surgery and randomize to receive standard-of-care single shot nerve block or the same block plus 5 day regional nerve block. .
   2. Follow-up subjects to obtain pain ratings related to the operated ankle, and screen for potential problems.

5. **Background:**

   Preclinical studies: When nerves are injured or transected, abnormal spontaneous activity develops at the injury site and within the cell bodies of the peripheral sensory nerves [1, 2 , 3]. A wealth of preclinical research studies [4, 5] including many from our laboratory [6-9], using a variety of pain models, shows that blocking this spontaneous activity early after the injury, for 5 to 7 days, strongly reduces or completely prevents development of chronic pain behaviors

and other long-lasting cellular abnormalities. This literature suggests that pre-emptive peripheral analgesia, applied in conditions with a known initiating event such as surgery or trauma, should be highly effective in reducing chronic pain. However, clinical studies of pre-emptive analgesia have had mixed results. We propose that the failures in such studies are in part due to a disconnect between the preclinical and clinical studies. Specifically: (1) Many clinical studies of pre-emptive analgesia have used primarily centrally acting analgesics such as opioids, which preclinical studies suggest would not be effective in blocking the critical changes and spontaneous activity occurring in peripheral sensory nerves and cell bodies. (2) Many clinical studies used pre-emptive analgesics for only 1 – 3 days, while preclinical studies suggest 5 – 7 days may be necessary to block development of chronic pain[6].

Clinical studies: Regional anesthesia techniques provide an excellent method for blocking nerve signals where they originate, in the peripheral nerve, which preclinical research suggests should be ideal for blocking development of chronic pain, in addition to blocking acute pain in the immediate post-operative period and reducing postoperative opioid use with its concomitant problems. Trauma care, rather than surgical care, has led the way in adopting regional anesthesia methods. Military medicine has been a leader in this regard, improving regional anesthesia and introducing it into field hospitals and enroute care, revolutionizing the care of soldiers injured in combat in the Iraq and Afghanistan conflicts [10, 11]. Military medicine studies have demonstrated the safety and efficacy of regional anesthesia for combat wounds, especially for managing surgical and acute postoperative pain [12, 13]. However, controlled research on the effectiveness of regional anesthesia in preventing development of chronic pain syndromes is difficult in the combat situation. Many wounded soldiers have had regional anesthesia lasting at least 5 – 7 days, without serious anesthetic complications, but under field conditions the interval between injury and starting regional anesthesia could not be controlled or in some cases even documented, the duration of regional anesthesia was not controlled, and long term follow-up was not always conducted to investigate chronic pain development. This pilot study will more systematically test the hypothesis that local nerve blockade will reduce the incidence of chronic pain following ankle fracture surgery. Ankle fracture, which was chosen as a defined proxy for peripheral trauma, results in a relatively high incidence of chronic pain conditions which have important long term negative effects on quality of life in 20% to 50% of patients [14-16].

Significance: Chronic pain affects over a third of adults in the United States, and for many patients treatments are ineffective [17]. Up to 81% of survivors of combat trauma have chronic pain conditions [18]. Trauma and surgery can be precipitating causes of chronic pain syndromes. This pilot study will test the hypothesis that regional anesthesia continued for a longer time than commonly used, may reduce the incidence of chronic pain conditions. If successful and confirmed in a larger study this work will contribute to readily implemented

changes in medical practice that may reduce development of chronic pain conditions after trauma and surgery.

6. **Study design:**

This is an investigator-initiated, single-center, prospective, non-blinded, randomized pilot study. We are requesting authorization to enroll up to 60 patients to allow for 40 evaluable subjects.

Adults undergoing surgery for open reduction and internal fixation for traumatic ankle fracture will be invited to participate in the study comparing the 2 forms of nerve block. All patients are currently given the option of popliteal nerve block (single injection of ropivacaine given just prior to surgery), which helps provide pain relief in the immediate postoperative period; the surgery itself is done under general anesthesia. Participants who have agreed to have the single shot procedure will be randomized into the control group (standard-of-care single injection of local anesthetic just prior to surgery) or experimental group (standard-of-care single injection plus 5 day ambulatory popliteal nerve block).

Standard-of care procedures for placement of the popliteal nerve block are as follows: The blocks are performed in the Same Day Surgery (Pre Op Holding Area), by Anesthesia Residents with direct supervision by Anesthesia Attending Faculty. All residents performing blocks are at training level PGY2 (second year resident) or above. Monitors utilized for block placement will be EKG, SpO_2, and Non Invasive Blood Pressure monitor. Standard ASA monitors are on the patient for the block. Supplemental oxygen is in every room as needed. A Code Cart is readily available in SDS and PACU for resuscitative measures if needed (rescue medications, ACLS Medication). A Lipid rescue agent (20% Intralipid solution) is available at all times in the OR Pharmacy (right next to Same Day Surgery). A difficult airway cart is available in PACU and SDS as well for any need for managing the airway. If there is a minor vascular injury (inadvertent needle puncture of the artery) the needle is repositioned prior to the injection. The single injection for popliteal nerve block generally consists of 20 ml of 0.5% ropivacaine. As part of standard care, patients sign a separate clinical consent form specifically for lower limb nerve block procedures.

In the experimental group, in addition to the standard single shot nerve block, subjects will receive a catheter to deliver continuous 5 day popliteal sciatic nerve block using a disposable ambulatory pain pump. The catheter will be inserted starting just prior to surgery. This procedure is readily added on to the procedure for single injection, which involves ultrasound (and in some cases nerve stimulation) guidance for insertion of a needle near the sciatic nerve at the popliteal fossa. As part of standard care for administering a peripheral nerve block, sedatives are administered on as needed basis. Typically the patient will receive midazolam 1 mg every 5 minutes as needed. The catheter is inserted

just after the nerve block injection, during the same procedure and using the same needle placement. If there is a major vascular injury during the catheter placement (placement of the peripheral nerve catheter into the artery as confirmed by withdrawal of blood from the catheter itself), the catheter will be withdrawn and the subject will not receive a pump. An ambIT portable pump (as currently used in the participating hospitals after some other types of surgeries) will be attached to the catheter at the time the block is placed, and continuous block with 0.2% ropivacaine will begin immediately after surgery. The drug delivery rate will be 6 mL/hour. An 800 mL bag of medication will be provided to the subjects to allow medication for a 5 day period without requiring the subject to return to the clinic for refill. This drug delivery rate is on the lower end of the range commonly used in our hospitals for patients taking home pumps after other types of surgeries, which are usually started at 8 mL/hour with the option of patient controlled boluses. Previous clinical studies examined infusion rates of 6 to 14 mL/hour. The lower, fixed rate was chosen for this study to help avoid toxicity, since the duration of the pump is longer than commonly used at our hospitals. The goal based on preclinical studies is to block abnormal spontaneous activity from the sensory nerves, which requires a lower dose than complete sensory block. The selected infusion rate should also avoid motor block. The daily dose will be 384 mg; the FDA data sheet [19] indicates that a cumulative dose of up to 770 mg over 24 hours is well tolerated and studies indicate that the peak systemic levels during prolonged infusion occur after approximately 3 days[12].

Subjects with more medial ankle fractures, in whom some of the affected region may lie outside of the popliteal distribution, will be eligible for the study. As part of standard care, such patients generally receive either a second single shot nerve block (saphenous) or rely on opioid anesthesia, depending on the preference of the anesthesiologist. Such patients will still receive only a popliteal continuous nerve block after the surgery. Since preclinical and clinical studies indicate that chronic pain rarely develops in purely sensory nerves such as the saphenous, we consider it consistent with the primary hypothesis to include such patients. The characterization of the fracture will be included in the clinical information captured by the study.

The infusion pumps and 800 mL bags of ropivacaine will be provided by the UC Health Investigational Pharmacy at the University of Cincinnati Medical Center. The ropivacaine 0.2% 800 mL bags will be compounded by certified pharmacy technicians and registered pharmacists in a certified ISO Class 5 biologic safety cabinet within an ISO Class 7 buffer room at the University of Cincinnati Medical Center consistent with USP 797 standards and American Society of Health-System Pharmacists (ASHP) guidelines [20]. The bags will be prepared by combining four, sterile, preservative-free, commercially available ropivacaine 0.2% 200 mL bags/bottles[21] (stable at controlled room temperature up to manufacturer's expiration date) into a 1,000 mL empty sterile bag (e.g., Baxter Viaflex bag) using a single sterile fluid transfer set. Using aseptic technique, the

infusion spike of the sterile fluid transfer set will be inserted into each commercial bag/bottle to drain completely (including any overfill) into the empty sterile bag via single needle manipulation of the injection port. After the fourth bag/bottle is drained, the needle and transfer set will be disconnected from the compounded bag, and the injection port will be aseptically covered with a foil seal. A total of 4 to 8 ropivacaine 800 mL bags will be batched at a time. Compounded ropivacaine 0.2% 800 mL bags will be dispensed by the inpatient investigational pharmacy following a patient-specific order from a research provider.

There are no additives in the final ropivacaine 800 mL bag that would affect stability beyond that of the commercial product. In order to ensure the sterility of the ropivacaine during the 5 days of use, the following procedure will be used: The final ropivacaine 800 mL bags will be considered medium-risk compounded sterile products (CSP). In lieu of a separate sterility test, USP 797 guidance indicates medium-risk CSPs should have a beyond use date (BUD) of 30 hours when stored at room temperature. To extend the BUD, sterility testing will be performed on each batch of ropivacaine 800 mL bags. Two of the bags in each batch will be tested for sterility using the QT JuniorTM System (Q.I. Medical, Inc., Grass Valley, CA, USA), which utilizes a 0.22-micron filtration set and fluid thioglycollate growth media [22]. The batched bags will remain quarantined before use for 14 days after preparation. On day 14, the QT systems being incubated from the 2 tested bags will be visually inspected for turbidity per the manufacturer instructions. If no turbidity is seen (i.e., negative growth) at day 14, then the batched bags will be released for dispensing for an additional 14 days (i.e., 28 days total from preparation: 14 days quarantined plus 14 days post-release) while being stored at controlled room temperature in the investigational pharmacy until dispensed or expired. Released bags will only be dispensed if the BUD does not extend beyond the planned 5-day therapy for a specific patient. Following the patient-specific dispense, the ropivacaine bag and pump will be connected directly to the nerve block catheter at the time the catheter is inserted, in the same day surgery area immediately after the single popliteal nerve block is administered. The catheter will be infused using a commercially available ambulatory infusion pump consistent with standard clinical care. Infusion will begin immediately after the surgery, when the patient is in the PACU.

Subjects will be contacted by phone each day by the study nurse or other clinical study member. The script to be used for this follow-up is provided in a separate document. This allows monitoring for post-operative analgesic use, toxicity, infection, or other problems related to the use of the pump, and for reminders about when and how to remove the catheter.

The treatment will be open label due to the impracticality of blinding the physician or patient to the presence of local anesthetic in the 5 – day pump and the ethical barriers to subjecting patients to implantation of a catheter and empty or saline pump with no benefit to them. Per standard of care, patients in both the

experimental and control groups will also have other oral pain medications prescribed for use as needed.

Additional data routinely obtained for clinical purposes will also be collected including demographic variables, opioid use in the PACU, pain medications prescribed at discharge, and type of ankle fracture. Standard database templates will be used to record information from the medical record where appropriate.

The patients randomized to the 5 day pump group will be undergoing an experimental procedure: ambulatory pumps for peripheral nerve block (including popliteal) are already successfully used in our clinics (with patients taking the pumps home and doing the removal of the catheter there) in the context other surgeries; but this is not routinely done for ankle fracture surgery nor for the indication of preventing development of chronic pain. In addition, normally the pumps are used for a shorter period of time.

The standard follow-up appointments with the orthopedic surgeons following ankle surgeries are at 10 - 14 days, 5 – 6 weeks, and 3 – 4 months. These visits will allow for monitoring of unexpected problems in patients receiving the pumps. In order to have consistent monitoring, a single orthopedic doctor will review the charts of all the enrolled patients in the experimental group on a regularly scheduled basis (at least monthly). As per our grant proposal patient charts will be reviewed for up to 3 months after use of the pumps. In addition, Dr. William Hurford will act as medical monitor for the study. He will review subject's research data and adverse events to ensure patient safety. The medical monitor will have the power to temporarily or permanently halt enrollment, if it is deemed that patient safety is compromised.

Subjects will be contacted at approximately 14 days and 3, and 6, and 12 months following the surgery to complete a pain questionnaire, the SEFAS (Self-Administered Foot and Ankle Questionnaire). The SEFAS is designed to evaluate disorders of the foot and ankle. It does not require physician input, and a study of its use after surgery found it to be a valid, reliable, and responsive patient-oriented outcome measure [23]. It consists of 12 questions focusing primarily on pain and its functional impact on daily life activities [24], meeting the new recommendations to use functional and patient centered outcomes in clinical research on pain [25]. Subjects will also be asked to provide information about their medication use including pain medications, at each of these time points. The consent form is structured to allow access to the medical records to obtain information about relevant clinical variables such as medications prescribed, complications, and diagnoses of chronic pain conditions.

The follow-up contacts to obtain questionnaire data will be made according to the subject's preferred contact method. Surveys will be available for subjects to complete on the internet, or via paper copy mailed to them or via telephone, as per their preference. For survey time points that coincide with the orthopedic

doctor's follow-up, Dr. Southam, the orthopedic surgeon involved with the study, may administer the survey.

7. Research data collection/study procedures:

Encounters: Consent and randomization will occur before the ankle surgery. For subjects in the experimental group, the catheter will be inserted just before surgery in conjunction with the standard-of-care single shot popliteal nerve block procedure, and local anesthetic perfusion will begin immediately after the surgery. All subjects will be contacted via their preferred method of contact to complete the pain survey (SEFAS) at 2 weeks, 3 months, 6 months, and 1 year after the surgery. Information about current pain medication use will also be collected at each of these time points.
Randomization: We will use a block-stratified randomization schedule with blocks of sizes 2 and 4. The West Chester and Uptown locations will have separate randomization schedules as it is thought the two locations provide somewhat different populations, making it desirable to have approximately equal numbers in the control and experimental groups at each site. Due to the requirement for quarantine of the ropivacaine prepared by IDS, subject randomization may sometimes deviate from the schedule: a subject scheduled to receive a pump may be placed in the control group if no ropivacaine is available at the time of their surgery, which will be compensated by placing a subsequent subject scheduled to be in the control group into the experimental group when drug is available. These deviations will not be based on subject characteristics, so that assignments remain random, and the total number of control and experimental subjects at each site will remain the same.
Data collection: We will establish an online copy of the SEFAS which subjects can use to enter their responses. This will be done using the REDCap (Research Electronic Data Capture) system for secure web based capture of questionnaire data. For patients opting to have a link to the SEFAS sent to their cell phones, the REDCap-Twillio integration platform will be used. Patients electing not to use the online entry format will be contacted by the research nurse via the preferred route indicated on the consent form, and the research nurse will then enter the data into the Redcap project database. Data from the questionnaires will be exported out of REDCap to be merged with the data from the Medidata Rave® database for analysis. All other data will be entered directly into the Medidata Rave® clinical database. Clinical demographic data will be obtained from the patient at the beginning of the study and verified with the electronic medical record. Analgesic use in the perioperative period will be obtained from the electronic medial chart. Patients typically receive acetaminophen and celecoxib preoperatively, then opioids postoperatively as needed. However, participating in the study will not affect the subjects' options for treatment for pain. Numerical pain ratings recorded in the PACU will be obtained from the electronic medical chart. The Verbal Numerical Scale (VNRS, 0 = no pain, 5 = moderate pain, 10 = worst possible pain) is used for patients in the

PACU and recorded in the electronic record, until the patient is discharged from the PACU. Chart review of the follow-up orthopedic appointments will be used to identify possible development of chronic pain conditions or unforeseen complications of 5 day pump use.

8. Specimen collection: not applicable.

9. Potential Benefits:
Possible benefits to the subject during the time the pump is in use include better postoperative pain control, improved sleep, and reduced need for opioids with their concomitant side effects and risk of abuse [26]. Preclinical data (see above) and some clinical data in other conditions provide some support for the hypothesis being tested that the nerve block will reduce the risk of chronic pain [27]. If this pilot study is successful and can be extended to a full study large enough to fully test this hypothesis, the research may contribute generalizable knowledge to improve practices in combat medicine and trauma medicine.

10. Potential Risks, Discomforts, and inconveniences:

Level of risk: Greater than minimal risk

We consider the risk level of the study to be low because the experimental treatment (ambulatory regional nerve block with ropivacaine) is already routinely used in other clinical conditions including at our clinic. A recent review stated that “Serious and permanent complications related to cPNB [continuous peripheral nerve block] are rare, whereas minor complications occur with a frequency similar to single-injection peripheral nerve blockade” [27](i.e., standard of care arm in our proposed study). Use of 5 day ambulatory pumps in postsurgical patients has become standard care at the Cleveland Clinic. They use the same device (Ambit) and drug (0.2% ropivacaine) that we propose to use, at a somewhat higher dose (8 mL/hour with 12 mL bolus-on-demand per hour, with reprogramming allowed if pain control was inadequate; compared to our proposed 6 mL/hour without bolus). Their standard of care is to have the patients use the pump for 5 days, turn them off for 6 hours, and then remove the catheter and pump if pain scores are less than 5, otherwise to restart the infusion. In their retrospective study [28] of the safety of longer duration perfusions, the median duration of pump use was 5 days (shorter durations generally only occurring in patients who had to remove the pumps) and some patients used the pumps longer than this. For the 290 popliteal blocks they report on, the median duration was 5 days and inter-quartile range was given as 4, 7. Similar to clinical practice at our institution, and as proposed in our study, patients using pumps at home were contacted each day by the Acute Pain Service to check for pain control, signs of infection, and signs of nerve damage or systemic toxicity. The conclusion of this study was that “prolonged use of ambulatory catheters for a median period of 5 days did not lead to an increased

incidence of complications". Specifically for the 290 patients receiving popliteal catheters, 3 complications were reported. Two patients had superficial infections at the catheter site which resolved with catheter removal (one of these was diabetic; our study excludes diabetic patients and this is known to increase the likelihood of such infections). One patient had pharmacological complications (ringing in the ears during the initial injection, resolved with no intervention). No complications indicative of nerve damage were observed in any of the patients with popliteal catheters.

One primary risk of the ambulatory pump is vascular puncture allowing the local anesthetic to enter the general circulation. Ultrasound guidance and (if also needed) peripheral nerve stimulation techniques are routinely used for inserting the catheters in order to minimize this risk[29]. Vascular puncture would likely occur during the standard-of-care initial single shot nerve block, not during the experimental 5 day pump procedure; and would be detected in the hospital setting with rescue medications and procedures available. A second source of risk is systemic toxicity even from a properly placed nerve block, leading to CNS symptoms including seizures or cardiac symptoms. Previous studies of long term regional nerve blocks in trauma patients have demonstrated that systemic ropivacaine levels start to decline after 3 days, and ropivacaine infusion even lasting much longer than the proposed 5 days does not lead to toxic levels of the drug in plasma [12]. Military medicine studies have demonstrated the safety and efficacy of regional anesthesia for combat wounds, especially for managing surgical and acute postoperative pain [12, 13]. As described in these studies, many wounded soldiers have had regional anesthesia lasting at least 5 – 7 days, without serious anesthetic complications, albeit but under field conditions in which the conditions and effect on chronic pain development could not be rigorously controlled. Some of the exclusion criteria are based on higher risk of toxicity per the drug manufacturer's information [30]. Another risk is of infection of the catheter site which rarely may lead to systemic infection. This risk increases with duration of the catheter use. In a study in orthopedic surgery patients using similar mean duration to what we propose [31] the overall risk of local inflammatory signs was 3%.

More Common Risks of peripheral nerve block and continuous peripheral nerve block:

Bleeding/blood aspiration (0.4%) [32]
Local Infection 0 – 3% [29, 31]
Paresthesia (short term; 0.5% - 1.5%) [31-33]
Inability to perform injection (see section 14 below)
Ineffective block (see section 14, below)

Extremely Rare Risks:

Nerve damage (short duration)
Muscle atrophy
Worsening of pain

Permanent or long-lasting nerve damage 4-7/10,000 blocks[27]
Local anesthetic systemic toxicity- (0.7 per 10,000)
Cardiac arrest (<1/100,000 with no deaths in several studies of >100,000 peripheral nerve blocks) [29, 34]

Clinical trial monitoring will be conducted to ensure that the rights and well-being of human subjects are protected, to verify that the reported clinical trial data are accurate, complete and verifiable from source documents and to verify that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with Good Clinical Practices and with the applicable regulatory requirements.

Safety criteria for removing a subject from the study in the period before the end of the 5-day ambulatory pump use:

Prior to and during the popliteal nerve block and catheter placement: Subjects with a failed peripheral nerve block will not have a catheter placed and will not be included in the study (see Exclusions, below). Subjects will be discontinued and the catheter removed if there is inadequate view of the popliteal nerve under ultrasound guidance, paresthesias that do not resolve before the local anesthetic from the nerve injection takes effect, blood is present in the catheter during insertion indicating possible vascular injury, or one or more signs of local anesthetic systemic toxicity (LAST) (ringing in ears, metallic taste in mouth, lightheadedness, seizure, or cardiac compromise).

During Surgical Procedure and General Anesthetic – Subjects will be discontinued if there are one or more signs of LAST (listed above) or the catheter is inadvertently removed during the operation.

During immediate postoperative period in PACU – Subject will be removed if there are one or more signs of LAST (listed above) or if the catheter is removed inadvertently

After Discharge for period the pump is used: Based on the daily phone contacts, subjects will stop using the pump if there are, signs of local infection(after evaluation by the Acute Pain Service; subject would be called back into the hospital), or one or more signs of LAST (listed above). Subjects who experience paresthesias that cause them discomfort, or weakness that prevents them from participating in physical or occupational therapy, will be asked to return to the clinic for evaluation by an anesthesiologist. If these issues cannot be resolved (e.g. by lowering the dose), these subjects will have the catheter and pump removed. Subjects who must remove the pump early for any reason will be retained in the study for purposes of answering the pain surveys.

Defining and Reporting of Adverse Events:

Adverse event Definitions:

Adverse Event
Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.
An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

Suspected Adverse Reaction
Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Adverse Reaction
An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

Unexpected
An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

Serious
An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the

patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Life-Threatening

An adverse event or suspected adverse reaction is considered “life-threatening” if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Table of Causality Definitions:

Causality term	Assessment criteria*
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/ Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination

Unassessable/ Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

Table 9.4. Toxicity Grading Scale:

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness*	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling**	2.5 – 5 cm and does not interfere with	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

*In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
**Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Vital Signs *	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) ** (°F) **	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths	17 – 20	21 – 25	> 25	Intubation

* Subject should be at rest for all vital sign measurements.
** Oral temperature; no recent hot or cold beverages or smoking.
*** When resting heart rate is between 60 - 100 beats per minute. Use clinical judgment when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

Systemic (General)	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 gms/24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or > 800gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

Table 9.4 extracted from: Guidance for Industry, Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Trials, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research, August 2016

Treatment of cardiovascular and neurologic adverse events

- Local anesthetic systemic toxicity
    - Treatment will be initiated as recommended as the American Society of Regional Anesthesia and Pain Medicine, according to the society's checklist

Treatment will include: transfer to intensive care unit setting if not already in intensive care unit, continuous hemodynamic monitoring for at least 24 hours, appropriate airway management with assistance from respiratory therapy and a critical care consultant as needed, cardiovascular stabilization and assistance from a critical care consultant as needed, administration of Lipid Emulsion therapy, as per ASRA checklist in Appendix, Neurology consult for any observed systemic

neurologic toxicity (including change in vision, mental status change, persistent headache, seizure), Cardiology consult for any arrhythmias that persist greater than 30 minutes, beyond initial appropriate medical treatment, or result in hypotension with systolic blood pressure < 80mmHg.

Every adverse event, whether or not thought to be related to study drug, will be recorded and entered into the Medidata Rave® Case Report Form database.

Any medical condition present prior to study enrollment should not be reported as an adverse event, unless the medical condition worsens in severity or seriousness during the study. In this case it may be reported as an adverse event at the discretion of the Investigator.

The Investigator will review each event and assess its severity and relationship to the study treatment.

Criteria for stopping the study early:

Because this is a small study, criteria for stopping the study will not be based on statistical analysis but rather on the occurrence of any of the following serious adverse events in any of the subjects randomized to receive the ropivacaine pumps:

During immediate peri-operative period after pump has been connected:
A single serious adverse event of LAST requiring rescue medication, cardiac resuscitation, or transfer to the ICU.

During the 5 day period of ambulatory pump use:
A single serious adverse event of catheter site infection requiring hospital admission.
A single serious adverse event of LAST requiring hospital admission.

During the entire study period:
A single serious adverse event of any life-threatening adverse event deemed possibly related to the use of the ropivacaine pump.

Two subjects receiving pumps experiencing moderate adverse events of tinnitus and/or metallic taste in the mouth.

11. Data Safety monitoring plan and/or DSMB:

As discussed in section 6, the medical monitor, Dr. William Hurford, will review subject's research data and adverse events to ensure patient safety."

12. Data Analysis:

The primary outcome measure is SEFAS scores at the indicated time points. A secondary outcome measure is use of opioids in the immediate postoperative period.

Each SEFAS response has 5 ordinal response choices scored 0 through 4, with the lowest score (0) representing the most severe disability and the highest total score being 48. If subjects omit a question the score will be re-normalized; however, the Redcap interface will be designed to try to obtain an answer for each question. The Mann-Whitney test will be used to examine differences in the SEFAS scores at each time point. For analysis of SEFAS scores, the pilot study sample size of 20 per group is sufficient for detecting a difference in scores between groups of 9 points with a power of 0.8 and $\alpha = 0.05$ (using the standard deviation obtained from SEFAS use in an ankle surgery study[35]); this score would represent moving up one rank in 3/4 of the questions which would be a functionally meaningful improvement given the 0 – 4 ordinal scale employed. . Patients who are withdrawn from the study due to failure of the initial nerve block (see above) will be considered as screening failures; no follow-up data or questionnaire scores will be obtained. We consider that such a failure is unlikely to have any relationship to the chronic pain outcome we are studying. The same approach will be taken for patients who decide to withdraw from the study, or are withdrawn by the attending surgeon or anesthesiologist, after randomization but before the single shot nerve block procedure.

Patients lost to follow-up after the end of the 5 day nerve block will be analyzed with a per-protocol analysis. We consider that, since the follow-up begins after the end of the treatment and consists only of completing questionnaires, there is unlikely to be a bias towards the experimental or control group having increased numbers of drop-outs.

Patients who have to (or choose to) remove the pump before the entire 5 day treatment period will also be analyzed both an intent-to-treat analysis and a per-protocol analysis. The duration of pump use will be noted.

As this is a pilot study, one intent is to develop estimates of the likelihood of drop-outs and incomplete treatments, to aid in design of a full sized study.

13. Data storage and confidentiality (include sample storage if applicable)

The signed consent forms will be stored in locked cabinets at the Westchester or UCMC locations, accessible only to the study members who are qualified to obtain consents. A single subject log (copy attached) will be kept by the study coordinator for matching patient study number, names, medical record number,

and surgery date. Study numbers will be used to identify questionnaire and clinical demographic data. As noted above, SEFAS data will be entered in the REDCap system, which provides password-protected security and encryption.

All other data will be entered into the Medidata Rave® database, and SEFAS data will be exported from REDCap and merged with the Medidata Rave® data for analysis. The Data Management Center (DMC) will provide full data management support to the project. The DMC has dedicated space within the Division of Biostatistics and Epidemiology (DBE) within Cincinnati Children's Hospital Me. The DMC currently consists of three Managers of Data Management operations and 25+ staff members (Clinical Research Data Specialists, Clinical Research Database Programmers and Data Coordinators), five of which are Certified Clinical Data Managers. DMC staff are active members of the Society of Clinical Data Management, the Drug Information Association, and the Society of Clinical Trials and subscribe to Good Clinical Data Management Practices.

Neither Medidata Rave® nor REDCap databases will contain subject names. The subject's enrollment into the study will be noted in the Epic chart, including a notation about whether or not they received the 5 day pumps, so that treating physicians will be aware of this history. Only authorized study personnel will have access to the rest of the data. In response to our query, the REDCap staff indicated that the REDCap system was not the best tool for conducting some of the types of analysis proposed (such as Mann-Whitney). A subset of the data (at least 20%) will be verified for accuracy by the study monitor. Files exported from Medidata Rave® that are generated for analysis of the de-identifed data will be stored on the research server. This College of Medicine server is password protected so that only members of the Research Director's laboratory can have access, and the directory containing study data will be further restricted so only the researchers directly involved in the study have access. The server contents are automatically backed up several times per day and retained off-site for 30 days.

Once the study has been completed, the subject log will be destroyed and only the de-identified electronic data will be kept. Only study personnel will have access to the de-identified data except as required for regulatory oversight.

14. Study Population (Including age, number of individuals, inclusion/exclusion)

Sample Size - Up to 60 patients will be enrolled in this single site pilot study.

Inclusion criteria –

- Adult patients of either sex, age 18 to 65
- Referred for surgery for open reduction and internal fixation for ankle fracture

- Agreed to have a single shot local nerve blockade (routinely offered as part of the standard-of-care but declined by some patients)

Exclusion criteria:

- patients unable to give informed consent in English
- unable to complete surveys in English
- unable to understand instructions for using the pump in English
- unavailable for follow-up
- Scheduled to enter a rehabilitation facility after the surgery (due to difficulty in conducting the 5 days of safety monitoring phone calls)
- polytrauma, i.e. undergoing other surgeries or having other fractures related to the precipitating cause of the ankle fracture
- infection such as abcess or bacterial infection; mild colds or upper respiratory infections do not require exclusion.
- peripheral vascular disease
- diabetes
- undergoing chemotherapy
- pregnancy (ropivacaine is FDA pregnancy category B; pregnancy test is routine part of the surgical procedure unless the woman signs a waiver; patients who sign such a waiver instead of having a pregnancy test will not be eligible for the study, unless their medical record clearly indicates they have had a hysterectomy or tubal ligation.)
- lactating
- have heart disease or heart rhythm disorder or taking anti- antiarrhythmic drugs
- severe renal impairment (Class 3 or worse kidney disease)
- liver disease (cirrhosis or liver failure)
- ever had an allergic reaction to any type of local anesthetic
- taking therapeutic doses of anti-coagulants or anti-platelet therapy (prophylactic doses started because of the hospital admission are not an exclusion)
- taking antidepressants or other psychiatric medications (due to drug interaction risk per the ropivacaine data sheet)
- single shot local nerve block prior to surgery was ineffective (rare; see below)
- selected for neuraxial anesthesia rather than general anesthesia for the open reduction surgery (rare)
- already receiving chronic analgesic therapy for a separate chronic pain condition

Rarely, the single shot local nerve blockade given prior to surgery as standard-of-care is found to be ineffective, and surgery proceeds using only general anesthesia. The ineffectiveness of the single shot would indicate that the catheter placement was also likely to be ineffective. For such patients, the

catheter will be removed before the surgery and they will be removed from the study; attempting to re-position and re-test the catheter outside of the standard-of-care procedures was deemed to be undue risk. Patients with failed nerve block who were not randomized to receive the pump will also be removed to avoid bias in the analysis, and because the lack of the single nerve block might also have effects on the development of chronic pain.

Because the treatment period lasts only 5 days, patients who may possibly become pregnant during that time are allowed to participate.

15. Consenting process and plan

A typical schedule for the potential subjects is for them to be admitted to the emergency department, diagnosed with ankle fracture, then either admitted to the hospital or sent home, after being scheduled for surgery for open reduction and internal fixation of the fracture the next day. In order to identify potential subjects, the study coordinator or others listed on the IRB protocol who have Epic privileges will review the orthopedic surgery schedules at the participating hospitals to identify potential subjects. We have applied for an IRB waiver to do a preliminary research screening in the medical record to avoid approaching potential subjects outside the age range or with polytrauma or other excluded conditions. A paper prescreening form will be used, listing inclusion and exclusion criteria, to determine as far as possible from the medical chart of scheduled patients whether the patient is eligible. If the patient agrees to join the study, this document will be kept with the consent form; if not, the document will be used to document the reason for the screening failure or to note that the patient refused to participate. The form will then be shredded; the sex, age in years, and reason for not enrolling in the study will be the only data retained. The orthopedic surgeon and the anesthesiologist scheduled to conduct the surgery will be contacted to confirm that they are willing to have the patient enrolled in the study, before subjects are enrolled. We will introduce the study to both the Anesthesiology and Orthopedic Surgery departments prior to the beginning of the study. Patients who have passed the prescreening and who will come to the surgery after hospital admission will be contacted in their rooms to invite them to participate, prior to the scheduled surgery (but after patients have been admitted to the hospital from the emergency room if that is where they initially presented). Patients who are scheduled to come to the surgery from home will be contacted at home by telephone, if they have passed the prescreening. In both cases patients will be requested to arrive at least 30 minutes earlier than otherwise scheduled so that consent and enrollment can be done in the pre-operative period. Consent will be obtained before the anesthesiologist starts the standard-of-care nerve block procedure.

Subjects can withdraw from the study at any time per their desire or may be withdrawn at the discretion of the orthopedic surgeon or anesthesiologist. Any subject who withdraws will continue to receive standard-of-care including follow-

up appointments and access to pain medications, which are unaffected by the study protocol.

16. Compensation:
    Subjects will receive a $25 gift card as a token of appreciation upon completing each follow-up questionnaire (up to a total of 4 for $100 total). Payments will be made using the Greenphire system.

17. Subject costs:
    There are no direct costs to the subject. In case of injury or illness related to the study, the University of Cincinnati Medical Center will provide emergency medical care at no cost to the subject. The University of Cincinnati will review each case and determine on a case by case basis whether to reimburse any out of pocket expenses.

18. Literature cited (references should be limited to relevant and current literature pertinent to the proposed study)

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