**Statistical Analysis Plan**

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

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## A. Introduction:

This is a pilot study to determine whether prolonged continuous peripheral nerve blockade, given for a duration longer than is customary in clinical practice, can reduce the incidence of chronic pain after ankle fracture. Patients undergoing surgery for open reduction and internal fixation of ankle fractures 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 (Self-Administered Foot and Ankle Questionnaire, SEFAS). Subjects will be followed for one year, with SEFAS scores administered at 14 days, and 3, 6, and 12 months following the ankle surgery. Secondary outcomes are postoperative opioid use in the Post-Anesthesia Care Unit (PACU), and pain ratings in the PACU. Data will also be obtained regarding the feasibility of doing a larger study. Preliminary analysis of possible confounding variables will be conducted, but as this is a pilot study it is anticipated that there may not be enough subjects to yield significant findings about patient subgroups.

## B. Specific Aims and Hypotheses

Aim 1: Test the hypothesis that SEFAS scores at the one year time point are higher (better outcome) in subjects who received a ropivacaine pump compared to patients who received standard care. This is the primary outcome measure).

Aim 2: Test the hypothesis that SEFAS scores at earlier time points (14 day, 3 month, 6 month) are higher in subjects who received a ropivacaine pump compared to patients who received standard care.

Aim 3: Test the hypothesis that pain scores and total opioid use in the PACU are lower in subjects receiving the ropivacaine pump.

Aim 4: Conduct a preliminary examination of possible roles of confounding clinical and demographic variables, focusing on: severity of ankle fracture; sex; and body mass index (BMI).

## C. Study Design

This is an investigator-initiated, single-center, prospective, non-blinded, randomized pilot study. We are authorized 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 popliteal injection of local anesthetic just prior to surgery) or experimental group (standard-of-care single injection plus 5 day ambulatory popliteal nerve block).

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.

Standard-of care procedures will be used for placement of the single shot popliteal nerve block. 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 just prior to surgery. A portable pump 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 when the patient arrives in the PACU.

Additional data routinely obtained for clinical purposes will also be collected including demographic variables, analgesic use in the PACU, and details of the ankle fracture and surgery.

The standard follow-up appointments with the orthopedic surgeons following ankle surgeries are at 10 - 14 days, 5 – 6 weeks, and 3 – 4 months. Chart review of these follow-up appointments will be used to extract additional clinical variables.

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. 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. It consists of 12 questions focusing primarily on pain and its functional impact on daily life activities. Subjects will also be asked to provide information about their medication use including pain medications, at each of these time points.

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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
- likely to be unavailable for follow-up
- polytrauma; undergoing other surgeries or having other orthopedic injuries related to the precipitating cause of the ankle fracture
- infection
- peripheral vascular disease
- diabetes
- undergoing chemotherapy
- pregnancy or refusal to take pregnancy test, if of childbearing potential
- 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)
- 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

## D. Statistical Analysis Plan

For categorical variables, counts and percentages will be presented. As a check on randomization, groups will be compared using the Fisher's exact test. For continuous variables, mean, median, standard deviation (SD) and inter-quartile range (IQR) will be presented. Groups will be compared using the t-test, except that non-parametric methods will be used for variables distributed non-symmetrically.

D1. Aim 1:

Each SEFAS response has 5 ordinal response choices scored 0 through 4. With 12 items and with the lowest score (0) representing the most severe disability, the total score ranges from 0 to 48. If a subject omits one or more questions, the total score will be re-normalized to 48. Group differences in the SEFAS scores at the 12 month time point will be analyzed using the t-test or Mann-Whitney test, as appropriate.

Patients who are withdrawn from the study due to failure of the initial nerve block will be considered as screening failures; no follow-up data or questionnaire scores will be obtained. 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 drop-outs.

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

D2. Aim 2:

Group differences in the SEFAS scores will be analyzed using a t-test or Mann-Whitney test at the 14 day, 3, and 6 month time points...

D2. Aim 3:

The times the patient enters and is discharged from the PACU will be recorded. Discharge from the PACU is based on several criteria, one of which is adequate pain control. Hence duration of PACU stay is relevant to pain experienced by the subject but there may be non-pain related reasons for prolonging the PACU stay. Verbal pain scores on a scale of 0 (least painful) to 10 (worst pain imaginable) are recorded periodically by the nursing staff and entered into the chart; the timing of these entries cannot be expected to be completely uniform and patients with higher pain may be queried more often. Pain scores will therefore be summarized by an area-under-the curve analysis, using a score of 3 as a reference value. A simple average of all pain ratings captured in the PACU will also be examined. Both sets of values will be compared between experimental and control groups using the t-test or Mann-Whitney test, as appropriate.

Time and amount of opioid medications will be captured from the PACU record. Different opioid drugs will be converted into analgesic equivalents using the values presented at http://www.globalrph.com/narcotic.htm. Total equivalent opioid use will be compared between experimental and control groups using the t-test or Mann-Whitney test.

D4. Aim 4:

Demographic and clinical data will be compared between the groups to determine if values differ significantly despite randomization (table *** below). A preliminary analysis of possible confounding clinical variables that may influence the development of chronic pain will be conducted. Linear regression analysis will be used to examine the contributions of these 3 variables and the treatment group (experimental or control) to the SEFAS score at 12 months. It is expected that this small pilot study will lack the power to fully analyze confounders, but the analysis may be used to guide future, larger studies.

## E. Variables in the analysis data set with Definitions

| Description |
|---|
| Patient unique ID |
| Age at ankle surgery |
| Date of ankle surgery |
| Weight and height at time of surgery |
| Date of enrollment |
| Gender |
| Race |
| Ethnicity |
| Randomized to control or experimental group? |
| Ankle fracture: number of malleoli affected |
| Grade of injury (defined as :closed injury, or open injury with Gustilo Anderson classification grade 1, grade 2, grade 3a, grade 3b, grade 3cr) |
| Opioid medication use in PACU: time, agent, dose, and route for each administration |
| Times entered and discharged from PACU |
| PACU discharge status (home, rehab facility, hospital, AMA) |
| Verbal pain scores in PACU (0 – 10 scale) and times at which recorded |
| Surgical Hardware: number of plates implanted, length and number of screw holes of each. |
| Estimated blood loss during surgery |
| Pain medication prescription at discharge (drug, dose) |
| Start time of surgery |
| End time of surgery |
| SEFAS score (2 week, 3, 6, 12 month post surgery) |
| Subject-reported analgesic use (2 week, 3, 6, 12 month post surgery) |
| Dates of post-surgical follow-ups (FU) |
| Weight bearing recommendation at each FU (non, partial, full, other) |
| Weight bearing current status at each FU [full, assisted (cane, walker, boot), non (crutch)] |
| Pain status at each FU (none, mild, severe) |
| Pain medication prescriptions at each FU (drug, dose) |
| Wound healing status at each FU (dehiscence, cellulitis , deep infection, healing well, other) |
| Range of motion at each FU |
| Re-operation required? |
| Date of re-operation |

| |
|---|
| Indication for re-operation (infection, non-union, hardware failure, hardware removal, other) |
| Chronic pain conditions diagnosed at one year FU. |

## F. Variables to Create / Calculate

| Description |
|---|
| BMI |
| Area –under- curve (from pain scores in PACU) |
| Analgesic equivalents of prescribed opioids |
| Total length of all plates implanted |
| Total number of screw holes of all plates implanted |
| Duration of surgery |
| Duration of PACU stay |

## G. Data Sources

- EPIC chart review
- SEFAS scores exported from REDCap
- Opioid equivalency values: http://www.globalrph.com/narcotic.htm

## H. Software Used (with References) and Specialized Macros (with References)

Calculation of basic statistical parameters, t-tests, Mann-Whitney tests, and Fischer's exact test will be conducted using GraphPad Prism (GraphPad Software, Inc.) or SAS 9.4 (SAS Institute).

## I. Mock tables to be produced

Table 1: Descriptive table of demographics of experimental and control groups prior to intervention.

| Description | Control (N = ***)[1] | Experimental (N = ***)[1] | p value |
|---|---|---|---|
| Age at ankle surgery (years) | | | |
| Weight at time of surgery | | | |
| Height at time of surgery | | | |
| BMI at time of surgery | | | |
| Race | | | |
| Ethnicity | | | |
| Ankle fracture: number of malleoli affected | | | |
| Grade of injury (defined as closed injury, or open injury with Gustilo Anderson classification grade 1, grade 2, grade 3a, grade 3b, grade 3cr)[2] | | | |
| Time in surgery | | | |
| Estimated blood lost in surgery | | | |
| Number of plates implanted | | | |
| Total length of plates implanted | | | |
| Total number of screw holes in implanted hardware | | | |

[1]Mean, SD, median, interquartile range for continuous variables, number and % per group for categorical variables.
[2] Converted to ordinal scale 1 – 6

Table 2 Pain outcomes

| Description | Control (N = ***) | Experimental (N = ***) | p value |
|---|---|---|---|
| Opioid medication use in PACU: analgesic equivalents | | | |
| Time in PACU | | | |
| PACU discharge status (home, rehab facility, hospital)[3] | | | |
| PACU Pain score AUC | | | |

| | | | |
|---|---|---|---|
| Average Pain score in PACU | | | |
| SEFAS score (2 week) | | | |
| Pain medication use analgesic equivalents (2 week) | | | |
| SEFAS score (3 month) | | | |
| Pain medication use analgesic equivalents (3 month) | | | |
| SEFAS score (6 month) | | | |
| Pain medication use analgesic equivalents (6 month) | | | |
| SEFAS score (12 month) | | | |
| Pain medication use analgesic equivalents (12 month) | | | |
| Number (%) with any chronic pain diagnosis at 12 months | | | |

[3] Converted to ordinal scale 1 – 3

Table 3 Other outcomes

| Description | Control (N = ***) | Experimental (N = ***) | p value |
|---|---|---|---|
| Number (%) requiring re-operation | | | |
| Number (%) : Indication for re-operation (infection, non-union, hardware failure, hardware removal, other) | | | |
| Wound healing status at first FU (dehiscence, cellulitis , deep infection, healing well, other)[1] | | | |
| Wound healing status at second FU (dehiscence, cellulitis , deep infection, healing well, other) [1] | | | |
| Weight bearing current status at first FU [full, assisted (cane, walker, boot), non (crutch)] [1] | | | |
| Weight bearing current status at second FU [full, assisted | | | |

| | | | |
|---|---|---|---|
| (cane, walker, boot), non (crutch)] [1] | | | |

[1] Converted to ordinal scale