Title: “Perineural Local Anesthetic Administration With a Continuous Infusion Versus Automatic Intermittent Boluses”

Primary Investigatory: Brian M. Ilfeld, MD, MS (Clinical Investigation)

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Study Protocol and Statistical Analysis Plan

Specific Aim: To determine the relationship between method of local anesthetic administration (continuous with PCA vs. intermittent dosing with PCA) for continuous peripheral nerve block and the resulting pain control.

Hypothesis: The investigators hypothesize that, compared with a traditional fixed, continuous basal infusion initiated prior to discharge, perineural local anesthetic administered with variable automated boluses at a lower dose and a 5-hour delay following discharge will (1) provide at least noninferior analgesia during the period that both techniques are functioning; and, (2) will result in a longer overall duration of administration [dual primary end points].

Enrollment: Patients 18 years and older undergoing painful foot and/or ankle surgery will be offered enrollment.

Nerve Block placement: The nerve block site will be cleaned with chlorhexidine gluconate and isopropyl alcohol (ChloraPrep One-Step, Medi-Flex Hospital Products, Inc., Overland Park, KS, USA), and a clear, sterile, fenestrated drape applied. The ultrasound probe will be readied for use and placed to visualize the short-axis (cross-section) of the target nerve. A skin wheal will be raised at the catheter-placement needle's anticipated point of entry. An 8.9 cm, 17-gauge, insulated needle (FlexTip, Arrow International, Reading, PA, USA) will be used to place all perineural catheters. The catheter-placement 17G needle will be inserted through the skin wheal, advanced in-plane beneath the US transducer and directed toward the target nerve. Normal saline (1-2 mL) will be administered via the needle to open the space around the nerve.

A flexible non-stimulating perineural catheter (FlexTip, Arrow International, Reading, PA, USA) will be inserted 2-3 cm past the needle tip. After catheter insertion, Ropivacaine 0.5% (20 mL) will be administered via the catheter under ultrasound visualization. Sensation in the tibial and peroneal nerve distributions will be checked for anesthetic effect up to 15 minutes following initial local anesthetic bolus. A "successful" regional block will be defined as sensory- and motor-block onset in all expected nerve distributions within the 15 minutes following the local anesthetic injection.

The initial local anesthetic bolus may provide complete surgical anesthesia for the procedure. Patients who desire a general anesthetic or experience a partial block that is not adequate for surgical anesthesia will receive a general anesthetic. Additional boluses of Ropivacaine 0.5% and epinephrine may be given, if needed, via the perineural catheter.

Randomization: Subjects will be randomized to one of two treatment groups: (1) automated regular boluses (ARB) with a 5-hour delay or (2) continuous infusion initiated at discharge in a 1:1 ratio using computer generated lists sealed in opaque envelopes not opened until after the nerve has been identified and deemed appropriate for catheter placement.

Postoperative Procedures: Following completion of the procedure in the operating room, an infusion pump (Infutronix, Natick, Massachusetts) with a 500 mL ropivacaine 0.2% reservoir will be attached to the patient's perineural catheter. For patients in the continuous infusion group, the pump will provide a 6 mL/h basal infusion and a 4 mL patient-controlled bolus with a 30-minute lockout (standard at UCSD). For patients in the automated intermittent bolus group, the pump will provide an automatic 8 mL bolus once every 2 hours and have a 4 mL patient-controlled bolus with a 30 minute lockout. In addition, for those in the automated intermittent bolus group, the infusion pump will be set in a "pause" mode that delays initiation of the automated bolus doses by 5 hours (this can be over-ridden by patients if they would like to initiate their perineural infusion earlier than 5 hours).

Data Collection: Data will be gathered from the patients' electronic medical record, by telephone follow-up, and from the infusion pumps memory. Subjects will be contacted via phone for the six days following surgery to collect information regarding surgical pain (Numeric Rating Scale of 0 to 10, with "0" being no pain and "10" being the worst pain ever experienced), analgesic use, number of sleep disturbances due to pain, and satisfaction with pain control.

Statistics: This study will be powered for two primary end points: (1) the average NRS queried on postoperative day 1; and (2) the duration of treatment from when the infusion pump was initially turned on until the local anesthetic reservoir was exhausted. The dual hypotheses will be tested with a serial testing strategy, such that Hypothesis 2 will not be formally tested unless the conclusion of Hypothesis 1 is at least "noninferiority". Noninferiority will be assessed by comparing the lower limit of the 95% confidence interval for the difference on the NRS (range: 0 to 10) to a pre-specified noninferiority margin of 1.7 NRS units. This will provide evidence that the analgesia provided by the novel automated boluses is no worse than 1.7 NRS units compared to Continuous Basal infusion.

Baseline characteristics of the randomized groups will be summarized with means, standard deviations, and quartiles. Balance between groups will be assessed. Specifically, standardized differences will be calculated using Cohen's d whereby the difference in means or proportions is divided by the pooled standard deviation estimates. Any key variables (age, sex, height, weight, and BMI) with an absolute standardized difference >0.47 (with $1.96\times\sqrt{(2/n)}=0.47$) will be noted and included in a linear regression model to obtain an estimate of the treatment group differences adjusted for the imbalanced covariate(s). If residuals from the linear regression indicate violations of key assumptions (i.e. homoscedasticity or Guassian distribution), data transformations and/or alternative generalized linear models will be applied as appropriate.

Secondary outcomes will also be analyzed by Wilcoxon-Mann-Whitney test, or linear models (or generalized linear models) as appropriate with covariates for any imbalanced covariates. No multiplicity adjustments will be applied for these analyses.

Sample size estimate: Power is simulated based on the distribution of pain measured with the Numeric Rating Scale (NRS) observed in previous studies. Specifically, the investigators simulate

NRS scores from a discrete distribution. This results in an expected interquartile range 1 to 4, and a median of 3 NRS units. 1000 trials were simulated in which the two groups, n=35 per group, were assumed to follow the same discrete distribution, submitted each trial to a Wilcoxon-Mann-Whitney test, and derived 95% confidence intervals. Out of the 1000 trials, 792 (79.2%) correctly resulted in a conclusion of non-inferiority; suggesting that the probability that the trial correctly concludes non-inferiority is about 80% when the groups follow exactly equivalent distributions.

If the test for Hypothesis 1 concludes noninferiority (scenario A, B, or C in Figure 1), the investigators will test for a difference in overall duration of administration again using the Wilcoxon-Mann-Whitney test.

Power is approximated by a two-sample t-test calculation. Assuming a standard deviation of SD=37 hours (corresponding to an interquartile range of 50 to 100 hours), the investigators expect that a sample size of n=35 provides 80% power to detect a mean group difference of 25 hours with a two-sided alpha of 5%.

Total enrollment: 70 subjects plus 30 for misplaced catheters or subjects otherwise unable to be randomized; and subjects who withdraw. This allows for a possible total of 100 subjects.