Study Protocol and Statistical Analysis Plan

Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-Amputation Pain

NCT01928849

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This randomized controlled trial was conducted as part of an ongoing collaborative research initiative (Veterans Integrated Pain Evaluation Research (VIPER)) between Duke University Medical Center, Walter Reed National Military Medical Center (WRNMMC) and the Durham Veterans Affairs Medical Center (VAMC). The trial was designed to determine the extent to which the addition of oral valproic acid to regional anesthetic blockade (either peripheral nerve or epidural) and multimodal perioperative care decreases the incidence of chronic pain 3 months after amputation or amputation revision surgery. We also analyzed the trajectory of pain and functional recovery after surgery as well as epigenetic mechanisms associated with the development of chronic pain after nerve injury. Findings from the epigenetic analysis will be reported separately.

Patient Recruitment:

Prior to enrollment, the clinical trial was approved by the respective institutional review boards at WRNMMC, Durham VAMC, and Duke University Medical Center and the trial was registered at ClinicalTrials.gov (NCT01928849). Patients scheduled for surgical amputation or revision were screened for trial participation at the three Medical Centers from 2013 to 2017.

Among those who were screened, a significant number had been added to the surgical schedules in a non-elective fashion at the Durham VAMC and Duke University Medical Center, and were not able to be approached for consent in a non-pressured environment given the short interim period between scheduling and surgery. Similarly,

patients scheduled for amputations following trauma were often excluded because of the urgency of surgery.

Inclusion/Exclusion:

Criteria for inclusion were individuals, age 18 years and older presenting for amputation, stump revision, or surgery for mangled limb (defined as limb injury with sensory or motor deficits consistent with injury to a major nerve).

Criteria for exclusion were severe traumatic brain injury, significant cognitive deficits or dementia of any cause, substantial hearing loss without alternative means of communication, spinal cord injury with permanent deficits, current pregnancy or lactation, end-stage liver disease or hepatic encephalopathy, current therapy with valproic acid or other valproates, coumadin, chlorpromazine, olanzapine, zidovudine, or monoamine oxide inhibitors (medications affected by valproic acid metabolism), diagnosis of seizure disorder requiring anti-epileptic medication, current therapy with tricyclic antidepressants doses greater than 50mg/day, current diagnosis of malaria requiring anti-malaria medication, or allergy to valproates or valproic acid.

Randomization:

After enrollment, randomization was performed within the respective investigational drug pharmacy according to the schedule provided by our statistician. Randomization was stratified by site and surgical intervention, ie, amputation, amputation revision, or surgery for mangled limb with equal probability of assignment to the valproic acid group

or the controlled placebo group. Patients, investigators, treating medical/surgical team, and study personnel were blinded to the assignment.

At each of the study sites, following randomization, an order was placed to the Investigational Drug Service (IDS). The IDS pharmacist then assigned treatment class according to the randomization schedule previously provided by the statistician. The pharmacist then dispensed the study medication (cherry-flavored liquid or similar flavored valproic acid liquid) in single-dose containers labeled with the patient ID# and no indication of the liquid contents. At the time of surgery, the labeled study medication was transported by the research coordinator to the patient in the pre-operative area where the first dose of medication was administered by the anesthesia team. Subsequent doses were delivered to the nurse on the patient ward or intensive care unit (depending on patient disposition). The IDS retained records of study drug inventory, dispensing records, and intervention allocation. Study drug reconciliation was closely monitored for compliance in the medication administration record. The Investigational Drug Pharmacist was the only person aware of treatment allocation until the close and unblinding of the study data for analysis.

Intervention / Treatment

The study medication (valproic acid oral solution 250 mg per 5 mL or placebo (similar tasting flavored syrup) was then administered in single-dispense units. The initial dose was given by the perioperative anesthesia team. Subsequent doses were stored on the hospital ward or in the ICU with the patient's other medications and administered by the

nurse every 8 hours, up to 7 days or until time of patient discharge from the hospital, whichever came first. Blinding was kept intact throughout the study for all patients.

Patients in both the placebo and intervention study arms received regional anesthesia (either peripheral nerve or epidural), with multimodal perioperative management according to the standard of care at each of the three institutions. Research blood samples were collected preoperatively, postoperatively (at the end of treatment with study drug or placebo), and at clinic follow-up (3 months or at time of adjudication). Valproic acid levels were measured at the completion of drug administration to confirm study compliance.

Clinical Assessment Tools:

Clinical assessments were performed at enrollment, daily during hospitalization, and at clinic follow-up (3 months). If a patient was not available at 3 months to collect adjudication data, the study outcome was determined at the 6-month research visit. Assessment tools for pain and function included the Numeric Rating Scale (NRS), a 0-10 integer scale of pain intensity where 0/10 represents no pain and 10/10 represents the worst imaginable pain, the Brief Pain inventory, short form(BPI) (1) and the Defense and Veterans Pain Rating Scale (DVPRS) (2). Phantom and/or residual limb pain was assessed using the Groningen Questionnaire Problems Leg Amputation (GQPLA) questions (3). Neuropathic pain was measured using the Self-Reported Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) tool (4,5). The presence of complex regional pain syndrome was determined using the Budapest Clinical Criteria

(6). Opioid and medication use was evaluated preoperatively, during hospitalization, and at the final outcome determination.

Physical Exam:

A physical exam of the surgical site was performed when possible, ie, without wound dressing). If a prosthesis was present, it was removed for the exam. If the site was not accessible at the 3-month follow-up visit, the exam was attempted again at 6 months. The exam included visual inspection for asymmetry of sweating, color, skin changes, and hair growth. Allodynia was tested with cotton wool brushing. The presence of a Tinel's sign was assessed by tapping on the most painful area and asking the patient if (s)he experienced any "sensations of pins and needles". Sensory and motor deficits were also noted.

Adjudication of Clinical Endpoint:

An adjudication committee consisting of Drs Buchheit, Van de Ven and Hsia met for 8 sessions between March 2014 and November 2017. All 3 members were required to be present for a quorum and a majority vote determined the phenotypic endpoint. At these meetings, the post-amputation pain subtypes were adjudicated using the Duke Post-Amputation Pain Algorithm (7).

STATISTICAL ANALYSIS:

Patient data were collected from patients at all study sites and entered into Research Electronic Data Capture (REDCap)^{TM}. Data were analyzed using SAS version 9.4 (SAS Inc., Cary, NC).

Patient characteristics were summarized by treatment group using mean (SD) or median [Q1, Q3] for numeric variables and count (%) for categorical variables to assess randomization and ensure balance between treatment groups. We also compared the patient characteristics between those who did and did not return for follow-up to evaluate the possibility of response bias. Finally, plasma levels of valproic acid (VPA) were monitored to verify treatment adherence, and to determine the concentrations of VPA among treated patients.

The incidence of chronic pain, the primary endpoint, was reported by treatment arm and compared using a two-sample chi-square test and multivariable logistic regression adjusting for baseline pain severity, type of surgery (amputation, revision, other), and surgical indication (medical vs. trauma). We also investigated possible differences in treatment effect within patient sub-groups based on study site, surgery type, and reason for surgery.

Secondary endpoints and analysis of functional trajectory were planned including the change in BPI (pain and interference scores), DVPRS (pain and supplemental scores), opioid use, and neuropathic pain subtypes from baseline to time of adjudication

endpoint. Median [Q1, Q3] of the changes of mean scales from baseline was computed by arm and by assessed time between the two treatment groups via Wilcoxon rank sum test, and overall by the Wilcoxon signed rank test. Frequency and percentage of the categorical variables in above endpoints was reported overall, by treatment arm, and by assessed time. Total opioid consumption during the first and second postoperative day was summarized via median [Q1, Q3], and compared between groups via Wilcoxon rank sum test. Rates of mortalities, liver disorders, and infections was summarized by group and compared by Fisher exact or chi-square tests as appropriate to evaluate safety of valproic acid administration.

Sample size was calculated for the primary endpoint based on the assumption that 65% of the non-treatment arm patients will experience significant chronic pain (NRS ≥3/10, averaged over previous week). We believed these estimates to be conservative, based on this group's prior research cohort (7) and prior literature demonstrating a phantom pain incidence as high as 79% in amputees from various causes Ephraim, 2005. With a 12% drop-out rate at 3 months secondary to death and loss to follow up, and a type 1 error rate of 0.05, the planned study of 224 patients would have 83% power to detect a difference in the incidence of chronic pain of 20% (45% vs 65%) between two arms using a two-sided chi-square test. Due to difficulties in enrollment the study was stopped early after 107 patients completed the primary endpoint evaluation.

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