Title: Minimization of Bleeding Related Adverse Drug Events in Plastic & Reconstructive Surgery

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Study Protocol

Patients

Eligible patients were 18 years of age or older, had a planned definitive plastic and reconstructive surgery operation under a general anesthetic, and had planned post-operative admission of at least two overnights. All patients had sequential compression devices placed in the OR and continued during inpatient admission. Patients were ineligible if they had any one of the following: contraindication to use of enoxaparin, intracranial bleeding or stroke, hematologic or bleeding disorder, known heparin-induced thrombocytopenia, creatinine clearance ≤30mL/min, serum creatinine >1.6mg/dL, epidural anesthesia, or patient/surgeon desire to be provided with non-enoxaparin chemical prophylaxis after surgery. Patients who received peri-operative aspirin were eligible for the study. Patients whose gross weight was >150kg were excluded. There was no minimum study weight. All patients provided written informed consent prior to their planned definitive operation.

Study Procedures

Patients were randomized immediately after their planned definitive operation, following a direct conversation between the Principal Investigator (CJP), primary plastic surgeon, and consultant surgeons or physicians. Primary surgeons had the discretion to decline study participation based on intra-operative events, such as procedure less invasive than planned or concern for intra-operative bleeding. Eligible patients were randomized to enoxaparin 40mg twice daily or enoxaparin 0.5mg/kg twice daily.

Investigational Pharmacy randomized patients and then provided study drug in identical syringes containing clear liquid; all doses were diluted to 1.0cc volume. Patients received the

first dose of study drug as a subcutaneous injection between 7 and 8 hours after the procedure ended, and every 12 hours thereafter until discharge from the hospital.

Patients had peak and steady state aFXa levels drawn after the third enoxaparin dose, at steady state. Goal peak steady state aFXa was 0.2-0.4 IU/mL. Investigational Pharmacy identified patients with out-of-range peak aFXa levels and performed real time enoxaparin dose adjustment. Dose adjustment was performed because initial low aFXa levels have significantly increased risk of VTE and high aFXa levels have been associated with bleeding. Therefore, not providing real time dose adjustment in response to documented aFXa levels would have been ethically marginal. Patients whose level was in-range continued on their initial enoxaparin dose until discharge. Patients who received real time dose adjustment underwent dose optimization until in-range peak aFXa level was achieved, and then received that dose until discharge.

Patients did not routinely receive post-discharge enoxaparin prophylaxis; this was provided only at attending physician discretion. When applicable, the resident physician received unblinded dose information, allowing the attending physician to remain blinded and objectively identify secondary outcome events while providing patients with a pharmacokinetically optimized dose.

The primary outcome (aFXa level in response to initial enoxaparin dose) occurred 36 hours after surgery, and could not be confounded by dose adjustment or receipt of post-discharge enoxaparin.

Patients received standard post-operative care from the primary surgeon. The study team contacted all randomized patients at 90 days to identify secondary outcomes.

Study Outcomes

Study outcomes were defined prior to enrollment of Patient #1, and definitions were published previously (Pannucci et al, "Double-Blind Randomized Clinical Trial to Examine the Pharmacokinetic and Clinical Imapacts of Fixed Dose versus Weight-based Enoxaparin Prophylaxis: A Methodologic Description of the FIxed or Variable Enoxaparin (FIVE) Trial", PubMed ID 31321183).

Both primary outcomes were pharmacokinetic outcomes derived from the initial peak steady state aFXa level, drawn at 36 hours after conclusion of the operation. The initial peak steady state level was in response to the initial enoxaparin dose; when dose adjustment was required, this level was not considered in the primary outcome. The primary effectiveness outcome was avoidance of under-anticoagulation (peak aFXa <0.20 IU/mL). The primary safety outcome was avoidance of over-anticoagulation (peak aFXa >0.40 IU/mL). Post dose-adjustment aFXa levels, if drawn, were not considered in the primary outcomes. Both secondary outcomes were obtained at 90 days after surgery. The secondary effectiveness outcome was 90-day symptomatic VTE, and the secondary safety outcome was 90-day clinically relevant bleeding.

Symptomatic VTE was defined as 1) any imaging-confirmed deep venous thrombosis (DVT) event, including upper limb, lower limb, or central, 2) any imaging-confirmed pulmonary embolus event, 3) any autopsy-proven VTE, and/or 4) 90-day mortality in which VTE could not be excluded (eg PEA arrest without autopsy). Patients were not screened for VTE events unless symptoms were present.

Major bleeding was defined using the published consensus definition of major bleeding for randomized controlled trials that examine anti-hemostatic drugs from the International Society of Thrombosis and Hemostasis. Major bleeding included any of the following events: bleeding requiring two or more units of blood transfusion, bleeding requiring bedside hematoma

evacuation or interventional radiology procedure, bleeding requiring unplanned return to the operating room, bleeding into a critical anatomic space, or fatal bleeding. In addition, we tracked clinically relevant bleeding, which was defined more broadly to include bleeding which required enoxaparin cessation in addition to all major bleeding factors.

90-day bleeding and VTE were compared between groups using a survival analysis log-rank test.

Outcome events were blindly adjudicated.

Statistical Analysis

The FIVE trial's sample size calculations and justifications were previously published (Pannucci et al, "Double-Blind Randomized Clinical Trial to Examine the Pharmacokinetic and Clinical Imapacts of Fixed Dose versus Weight-based Enoxaparin Prophylaxis: A Methodologic Description of the FIxed or Variable Enoxaparin (FIVE) Trial", PubMed ID 31321183).

Statistical analyses were performed using Stata15 (StataCorp; College Station, Texas).

We compared patient-level variables (Tables 1 and 2) between groups using student's t-test for continuous variables, chi-square or Fisher's exact test for dichotomous variables, and Wilcoxon rank-sum test for ordinal variables.

The primary effectiveness outcome was avoidance of under-anticoagulation (peak aFXa <0.20 IU/mL). Initial sample size estimates for under-anticoagulation avoidance were obtained

from a prior clinical trial, which established that 90.4% of patients who received enoxaparin 40mg twice daily were not under-anticoagulated. We assumed the rate of not being under-anticoagulated was 90.4% in the weight-based group. The primary effectiveness analysis was a noninferiority analysis with a two-sided test at the 0.05 level. The noninferiority margin was set at -12%. To achieve 90% power using a two-sided comparison with alpha of 0.05, using a two-sided 95% confidence interval around the difference in proportions, 127 patients per group were needed. The noninferiority hypothesis was tested by a Poisson regression model for binary outcomes with robust standard errors. After the Poisson model was fit, marginal estimation was used to calculate the 95% confidence interval around the difference in proportions. This method took the two estimated proportions used in the risk ratio, subtracted then, and computed the confidence interval for non-inferiority testing. To obtain a two-sided noninferiority test p-value, we used a Wald post-test to compare the difference in proportions to the noninferiority margin constant -0.12.

The primary safety outcome was avoidance of over-anticoagulation (peak aFXa >0.40 IU/mL). Initial sample size estimates for over-anticoagulation were obtained from a prior clinical trial, which showed that 72.2% of patients who received enoxaparin 40mg twice daily were not over-anticoagulated. We assumed that weight-based dosing would increase the proportion of patients not over-anticoagulated to 90%. To detect this difference with 90% power using a two-sided comparison with alpha of 0.05, 100 patients per group were needed. For this outcome, a Poisson regression model for binary outcomes with robust standard errors was fitted.

The Data Safety and Monitoring Board reviewed unblinded 90-day VTE and bleeding data every six months. To avoid an increased risk for type I error, no interim analyses were performed on primary outcomes.

After 254 patients were randomized, the study statistician reviewed unblinded data to determine the number of patients who did not produce primary outcome data. No interim statistical analysis was performed at this phase, to avoid an increased risk for type I error. The planned sample size was adjusted upward to 295, to include at least 127 patients in each group who produced primary outcomes data.