

Study Protocol and Analysis Plan

Fixed Versus Weight-Based Enoxaparin Dosing in Thoracic Surgery Patients

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Study Design

Inclusion criteria were thoracic surgery patients, surgery under general anesthesia, and prophylactic enoxaparin initiation within 24 hours. Exclusion criteria were creatinine >1.6mg/dL, planned postoperative admission <3 days, epidural catheter, history of heparin induced thrombocytopenia, known bleeding issue, weight >150kg, or recent stroke or intracranial bleeding event. Most open thoracic surgery patients at both sites receive concomitant epidural anesthesia; this biased our sample toward the video-assisted thorascopic surgery (VATS) population. Patients provided written informed consent.

The study was designed prospectively as a pre/post trial to examine the impact of a change in practice (a switch from fixed dose to weight tiered enoxaparin). Cohort 1 accrued between September 21, 2017 and May 8, 2018, and all patients received fixed dose enoxaparin prophylaxis at 40mg once daily. Cohort 2 was planned as weight based at 0.5mg/kg, and recruitment began on May 9, 2018. Both sites encountered insurmountable issues with pharmacist dose rounding. Nine patients in the 0.5mg/kg group who received rounded doses were dropped. Cohort 2 was revised to weight-tiered, daily enoxaparin¹⁵. Patients <70kg received 30mg, patients 70kg to 89.9kg received 40mg, and patients \geq 90kg received 50mg. Cohort 2 accrued between August 9, 2018 and March 25, 2019. Figure 1 describes patient enrollment, exclusion, allocation, and followup.

We examined enoxaparin pharmacokinetics using steady state peak and trough aFXa levels, drawn at 4 and 12 hours after the third dose. Goal peak aFXa (0.3-0.5 IU/mL) was chosen to maximize VTE risk reduction while minimizing bleeding^{12,19}. All patients with identified out-of-range levels received dose adjustment and repeat aFXa levels per Figure 2. The algorithm targeted peak aFXa levels because low peak aFXa has been associated with symptomatic 90-day VTE⁹, because aFXa-driven dose adjustment is

impactful ⁸, and because a recent review showed that ~80% of studies targeted peak aFXa ^{19,20}. Dose adjustment was performed until an in-range peak level was achieved, or until time of discharge.

Patients received enoxaparin prophylaxis for the duration of inpatient stay. Post-discharge enoxaparin prophylaxis was not routinely provided; when given, patients were discharged on a pharmacokinetically optimized dose.

Study Outcomes

The primary effectiveness outcome was adequate peak aFXa (≥ 0.3 IU/mL), chosen because patients receiving enoxaparin 40mg once daily with initial peak aFXa < 0.3 IU/mL are at elevated risk for 90-day symptomatic VTE ⁹. The primary safety outcome was avoidance of over-anticoagulation (peak aFXa ≥ 0.5 IU/mL), which could increase risk for bleeding.

Secondary outcomes included 1) achievement of adequate trough aFXa level (aFXa ≥ 0.1 IU/mL), because low aFXa trough increases asymptomatic DVT risk ¹¹, 2) 90-day symptomatic VTE, and 3) 90-day clinically relevant bleeding. Symptomatic VTE was defined as any symptomatic deep vein thrombosis or pulmonary embolus with imaging confirmation. Screening duplex ultrasound was not performed, as suggested by current American College of Chest Physicians guidelines ². Clinically relevant bleeding was defined as any bleeding that changed the course of care ²¹; this included bleeding requiring enoxaparin cessation, unexpected transfusion, or procedural (interventional radiology or operating room) intervention. Chart review and mandatory phone calls at 90 days identified events that occurred at other facilities; when identified, records were obtained for confirmation.

Analysis plan

Study data were uploaded to a secure, online Research Electronic Data Capture platform.

Descriptive statistics compared patient level factors including individual VTE risk using the 2005 Caprini score ²² and surgical details, by group.

The proportion of patients who achieved the primary effectiveness and primary safety outcomes were compared, by group, using the chi-squared or Fishers exact test.

The survival analysis log-rank test compared 90-day VTE and 90-day bleeding, by group. No patient was lost to followup and the censoring rate of this survival analysis was zero.

Sample size calculation

Historical data showed that the two institutions admitted 14 eligible patients monthly. Similar studies showed that high proportions (~99%) of patients consented and 70% of these would produce primary outcome data ^{8,9,14}. We estimated that 116 patients (58 per group) could be consented within the planned 12 month study period.

We assumed 32.6% of thoracic surgery patients receiving enoxaparin 40mg once daily would have adequate anticoagulation (peak aFXa level ≥ 0.3 IU/mL) ⁸, and that 82% of patients would have adequate anticoagulation in response to once daily weight-tiered enoxaparin dosing, based on data from women having caesarean section ¹⁵. Using alpha of 0.05 and beta of 0.9, at least 23 patients per group would be required. Thus, anticipated recruitment exceeded the minimum number of required patients.

Based on existing trials data from thoracic surgery patients receiving enoxaparin 40mg once daily ⁸, low (~1%) rates of 90-day VTE and bleeding were anticipated. Thus, it was impossible to adequately power the study for a clinical endpoint.

