# Weight-Based Enoxaparin Dosing and Real-time Dose Adjustment in Orthopaedic Trauma

## Protocol Summary

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## Background and Introduction

Venous thromboembolism, which encompasses both deep vein thrombosis (DVT) and pulmonary embolism (PE), is a potentially devastating post-operative complication. VTE results in approximately 100,000 deaths per year, a number higher than the annual mortality from breast cancer and motor vehicle accidents combined[1-3]. PE results in 5-10% of hospital deaths, making it one of the most common preventable causes of in-hospital death[1,4]. The rates of VTE after orthopaedic surgery are as high as 40-60% without prophylactic measures[4]. Polytrauma, older age, obesity, prolonged operative time, and prolonged bed-rest are some factors that put surgical patients at higher risk. Enoxaparin chemoprophylaxis has been shown to result in a four-fold reduction in DVT rates in post-operative orthopaedic trauma[5].

The American College of Chest Physicians (ACCP) and American Academy of Orthopedic Surgeons (AAOS) have issued guidelines for thromboprophylaxis following total knee arthroplasty, total hip arthroplasty, and hip fracture surgery (HFS)[6,7]. These guides lack specific recommendations for other high-risk injuries including pelvic, acetabular, or femur fractures. The Orthopaedic Trauma Association (OTA) has published an expert panel consensus on prophylaxis in the orthopaedic trauma population, however[8]. Even with these guides though, the optimal strategy to prevent post-operative VTE remains unclear. Drug choice, drug dosing, duration of prophylaxis, and the degree of anti-coagulation are all still debated. The 2012 ACCP guidelines in HFS, for example, recommend the use of one of several agents including low molecular weight heparins, unfractionated heparin, warfarin, or aspirin for 10 to 35 days, leaving the surgeon left to decide the exact drug and duration[6]. The OTA and AAOS favor enoxaparin as drug of choice, but are equally non-specific on duration and make no recommendations for specific orthopaedic injuries[7,8].

Enoxaparin, a low-molecular-weight heparin (LMWH), produces an anticoagulant effect by binding antithrombin, thereby accelerating antithrombin's inactivation of coagulation factor Xa (FXa), thus decreasing the likelihood of clot formation. Current recommended prophylactic dosing of enoxaparin is either 30mg twice daily (BID) or 40mg daily (QD). While not currently part of the standard of care, steady state peak and trough anti-Factor Xa (aFXa) levels can be used to monitor enoxaparin activity[9,10]. On twice daily dosing, a steady state peak range of 0.2-0.4 IU/mL and trough of > 0.1 IU/mL have been shown to maximize VTE risk reduction in non-orthopaedic populations[10-13].

Despite standard dosing enoxaparin prophylaxis, VTE rates in post-operative orthopaedic trauma patients remain as high as 12.2%[5]. It is not known why some patients suffer from breakthrough VTE events despite standard prophylaxis. Current prophylaxis guidelines do not adequately address these individuals[6,7]. The use of standardized enoxaparin dosing is has been challenged by a data from a prior study by this group as well as several other surgical fields. Body weight and the extent of thermal or surgical injury have been shown to correlate with anti-Xa levels in thermally injured, critically ill, and obese patients[12-16]

**Unpublished data from prior study on standard enoxaparin dosing in orthopaedic trauma**

From May 2016 to May 2017, 109 unique post-operative orthopaedic trauma patients were enrolled and obtained appropriately timed peak aFXa levels. Fifty eight (53%) had initial peak aFXa levels within the goal range of 0.2-0.4 IU/mL while 15 (19%) had initial aFXa trough within goal range >0.1 IU/mL. Real-time dose adjustment was successful in achieving goal peak aFXa in and additional 14 of 20, resulting in 72 of 109 (66.1%) achieving goal steady-state peak aFXa levels. Ninety-eight patients (89.9%) were discharge from the hospital on some duration of outpatient enoxaparin, 25 (25.5%) of which were receiving doses that were inadequate based on aFXa level (aFXa <0.2 IU/mL).

Eighty-eight patients have reached the 90-day mark post-operatively as of May 15, 2017. Eleven patients were lost to follow-up (no clinic visits and unreachable by phone) leaving 90-day follow up data available for 77 patients (87.5%). There were no re-operative bleed events and there were two minor bleed events while on anticoagulation, including one patient with a heavy menses and one with a positive guiac but no identified GI bleed.

Seven VTE events occurred, including 4 DVTs and 3 PEs in 5 patients (n 109, rate 4.6%). One DVT occurred in a patient who was within the goal peak aFXa range on initial blood draws (n 58, 1.7%). The remaining 6 VTE events occurred in 4 patients who had initial peak aFXa levels below goal range (n 47, 8.5%). Our data demonstrated that 43% of patients received inadequate prophylaxis in response to 30mg BID enoxaparin dosing and that a moderate correlation ($R^2$ = 0.46) exists between weight and peak aFXa in response to a fixed dose. Four patients were considered to be over anticoagulated (>0.4 IU/mL).

This study would examine if a weight based enoxaparin protocol could elevate the number of post-operative orthopaedic trauma patients receiving adequate chemoprophylaxsis. It aims to see if the orthopaedic trauma service can increase the number of patients that start on adequate prophylaxis and increase the number of patients that get discharged on appropriate doses. Two VTE events occurred while patients in the prior study were undergoing enoxaparin dose adjustment. These may have been avoided if the patients received an initial enoxaparin doses that were weight based rather than of standard dosing. Ultimately this study may aid in our understanding why breakthrough VTE events occur and hopefully become part of a means to reduce breakthrough occurrences.

## Purpose and Objectives

The American College of Chest Physicians and American Academy of Orthopaedic Surgeons recommend post-operative venous thromboembolism (VTE) prophylaxis in certain orthopaedic trauma patients to lower the risk of DVT and PE. 30mg twice daily (BID) or 40mg once daily (QD) of enoxaparin is commonly used as chemoprophylaxis and has shown efficacy in reducing VTE rates in post-operative patients. Based on steady state anti-Factor Xa (aFXa), a marker of enoxaparin activity, obese, critically ill, and thermally injured patients are often provided inadequate prophylaxis on these standard enoxaparin doses[9,10,12,13]. In joint replacement and trauma populations, inadequate steady-state aFXa levels have been associated with an increase in DVT rates[10,14,]. Despite enoxaparin prophylaxis, VTE rates remain as high as 12.2% in orthopaedic trauma. These events can represent a significant financial burden to hospitals and can be life or limb threatening for patients. Existing data from our group and others suggest that inadequate enoxaparin dosing, quantified by xFXa levels, represents a plausible explanatory mechanism for some of these "breakthrough" VTE events.

A previous study by this group examined the association between standard enoxaparin dosing (30mg BID) and steady state aFXa levels in orthopaedic trauma and found an association with inadequate aFXa levels and VTE events. A correlation was found between patient weight and their peak aFXa level. No association was found between aFXa and major bleed events. Based on these data, a weight-based protocol was adopted on for enoxaparin prophylaxis on the orthopaedic trauma service. The current study aims to examine how a weight-based dosing protocol alters the steady state aFXa in orthopaedic trauma patients as well as their risk for VTE and major bleed events.

Aim 1: Evaluate peak steady-state aFXa levels in response to weight-based enoxaparin prophylaxis (0.4mg/kg twice daily) in orthopaedic trauma patients.

Rationale: More than 12% of orthopaedic trauma patients experience breakthrough VTE events despite standard dose enoxaparin prophylaxis. Fixed dose enoxaparin prophylaxis has been shown to be inadequate in orthopaedic trauma surgery and several other surgical subspecialties. Prior data from this group showed that 53% of orthopaedic trauma patients were within goal peak aFXa range.

Hypothesis: Initial peak steady-state aFXa levels will be within the accepted range (0.2-0.4 IU/mL) in 75% of patients on weight-based enoxaparin dosing in orthopaedic trauma patients, up from 53% on fixed 30mg BID dosing.

Aim 2: Examine the response of aFXa levels to a real-time dose adjustment protocol.

Rationale: Literature in several surgical subspecialties shows that dose adjustment can significantly increase the number of patients within goal the peak aFXa range. Data from this group showed that dose adjustment achieved an increase in the number of patient within range

from 53% to 66%.

Hypothesis 2: Protocol-driven enoxaparin dose adjustment in response to aFXa levels will increase the proportion of patients with appropriate aFXa peak levels to from 75% to 85%.

Aim 3: Examine rates of 90-day VTE and clinically relevant bleeding events in orthopaedic trauma patients on weight-based enoxaparin prophylaxis.

Rationale: This observational aim will allow us to better understand VTE and bleeding rates after orthopaedic trauma surgery. Events have been shown to be rare and we recognize that the proposed study is underpowered to rigorously examine alterations in VTE or bleed rates in response to the proposed dose adjustment protocol.

Hypothesis 3: Rates of post-operative VTE and re-operative bleeds will be < 2% in each group.

## Study Population

**Age of Participants:** 18+

**Sample Size:**
At Utah: 137
All Centers:

**Inclusion Criteria:**
We will include adult patients who have undergone orthopaedic trauma surgery and can have enoxaparin initiated within 36 hours after procedure. All patients will undergo informed consent.

**Exclusion Criteria:**
We will exclude those with intracranial bleeding/stroke, bleeding disorder, heparin-induced thrombocytopenia, creatinine clearance ≤ 30mL/min, epidural catheter, or serum creatinine >1.6mg/dL.

## Design

Prospective Clinical Research

## Study Procedures

**Recruitment/Participant Identification Process:**

Daily operative schedule will be reviewed for University of Utah orthopaedic trauma surgeons to identify post operative trauma patients. Once identified, patients will be approached by Dr. Daniel Jones or the study clinical research coordinators (Kory Fleming, Andrea Gurule) to undergo the informed consent process.

**Informed Consent:**

**Description of location(s) where consent will be obtained:**

University of Utah Hospital

**Description of the consent process(es), including the timing of consent:**

Patients will be identified based on the daily surgery schedule and followed to see if they are started on enoxaparin post operatively at the discretion of the surgeon. Patients will undergo the informed consent process on post-operative day one or two while admitted to the hospital. No waiting period between the consent process and obtaining consent is planned, unless requested by the patient.

**Procedures:**

Patients will have enoxaparin initiated within 36 hours after the surgical procedure. The starting dose will be 0.4mg/kg. Blood draws will be a procedure performed in this study. After the third enoxaparin dose, patients will have peak and trough steady state anti-Factor Xa levels drawn. These will occur at 4 and 12 hours after the third enoxaparin dose, respectively. Patients with "in range" peak anti-Factor Xa levels (0.2-0.4 IU/mL) will have no additional lab values drawn and will have no dose adjustment. Patients with "out of range" anti-Factor Xa levels (<0.2 IUmL or >0.4 IU/mL) will have real time enoxaparin dose adjustment performed and will have repeat peak and trough steady state anti-Factor Xa levels drawn after the third dose. Most patients that require dose adjustment will only need it once. We anticipate a very small percentage of patients that will go through two or three rounds of dose adjustment. Dose adjustment for those under range will be a 10mg increase in their weight-based dose. Those over range will have a 10mg dose increase in their weight-based dose. Monitoring of aFXa levels will be discontinued when peak levels are in range, the surgeon discontinues enoxaparin prophylaxis, or the patient is discharged from the hospital. The enoxaparin doses used in this study are in accordance with the approved usages of enoxaparin and therefore do not require an IND.

All patients will also receive sequential compression devices for the duration of their inpatient stay, as per hospital policy.

Patients will be contacted via telephone or certified latter at 90 days after surgery to identify VTE or bleeding complications that were diagnosed or managed at other institutions.

**Procedures performed for research purposes only:**

The surgery is standard of care. The decision to have surgery or not is part of the standard care and has nothing to do with the research process.

Provision of post-operative enoxaparin is standard of care. The decision (yes/no) to give enoxaparin by the surgeon is not part of this study.

The non standard of care procedures for this study include:

1. Blood draws for anti-Factor Xa levels after surgery (generally 2-4 blood draws per patie

2. Possible Enoxaparin dose adjustment based on anti-Factor Xa level

## Statistical Methods, Data Analysis and Interpretation

The proportion of patients with in-range peak aFXa levels using fixed vs. weight-based dosing will be compared with the chi-squared test. The impact of real time enoxaparin dose adjustment will be examined by comparing the proportion of patients with in-range aFXa levels before and after dose adjustment. Time series analysis will examine associations between initial in-range and out-of-range aFXa levels and downstream VTE and/or major bleeding events.

Our projected recruitment results in inadequate power to examine VTE prevention or major bleeding events in response to enoxaparin dose escalation (one of our aims). This study will provide important preliminary data for weight-based dosing in orthopaedic trauma, which to our knowledge has not been done in orthopaedic surgery to date. We will collect data on 90-day symptomatic VTE events, 90-day major bleeding events (re-operative hematoma), and time to VTE or major bleeding event. We will contact patients at 90 days via telephone or certified mail to identify events that were diagnosed or managed at other institutions.

Sample size calculation:

Retention from our previous study in orthopaedic trauma was 72%. 151 patients were enrolled, 22 discharged prior to lab draws, 8 were changed from enoxaparin to an alternative blood thinner prior to lab draws, and 12 underwent blood draws but had unusable data as the draws were inappropriately timed (<3hrs or >5hrs after 3rd enoxaparin dose for steady-state peak xFXa level). Of these remaining 109 patients, 53% had initial peak aFXa levels within our goal range of 0.2-0.4IU/mL. Dose adjustment achieved adequate prophylaxis in an additional 13% of patients. Our hypothesis is that 75% of patients will be within range with weight-based dosing. Using an alpha of 0.05 and beta of 0.9, we would need 107 patients to effectively power a similar change for peak aFXa levels in the proposed study. With 28% over enrollment to allow for attrition, we would require n = 137.