Official Title: : Evaluation of Residual Anti-Xa Activity As A Function Of Time Following The Last Treatment Dose of Enoxaparin In Patients Presenting For Elective Surgery

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Study Title: Evaluation of Residual Anti-Xa Activity As A Function Of Time Following The Last Treatment Dose of Enoxaparin In Patients Presenting For Elective Surgery

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Background, Rationale and Context

Enoxaparin is a factor Xa inhibitor commonly used for both prophylaxis against and treatment of thromboembolism. It is also frequently used off-label as a perioperative bridge for patients that are chronically anticoagulated prior to surgery, such as those taking Warfarin. It is an attractive option for perioperative use secondary to its predictable pharmacologic profile and the lack of recommended routine blood monitoring. Therefore, it is common to encounter a patient who has recently received a treatment dose of Enoxaparin prior to presenting for surgery. For these patients, and those on other anticoagulant medications, published guidelines have been developed to help guide clinical decision-making when the anesthetic/analgesic plan includes regional anesthesia.[1]

Currently, these guidelines recommend that a minimum of 24-hours should elapse following the last treatment dose of Enoxaparin before a neuraxial procedure is performed. However, a recently completed quality improvement project conducted at Wake Forest Baptist Medical Center found that almost 60% of patients presenting for surgery while on treatment dose enoxaparin still had significant anticoagulant activity 24-hours following their last dose, as demonstrated by anti-Xa level assay testing. Given that the risk of epidural hematoma formation is increased in the setting of abnormal coagulation parameters[2], the significance of this finding is that the risk of bleeding complications following a neuraxial procedure may still be increased 24-hours after the last treatment dose of enoxaparin.

While the routine use of anti-Xa level testing may be a viable option to determine when residual enoxaparin activity is present before proceeding with a neuraxial procedure on a patient-by-patient basis, it is not universally available at all hospitals. Therefore, it is important to determine the time interval following the last enoxaparin dose at which the likelihood that a clinically relevant amount of residual anti-Xa level activity no longer persists, so that providers can confidently proceed with a neuraxial procedure when anti-Xa level testing is not available.

Objectives

The main objective of this study is to determine the time interval following the last treatment dose of enoxaparin at which the amount of anti-Xa level activity is reliably less than 0.2IU/mL in patients presenting for elective surgery.

Methods and Measures

Design

- This is a randomized prospective observation trial.

Setting

- This study will be conducted at a single institution (Wake Forest Baptist Medical Center), which is an academic level-1 trauma center.

Subjects selection criteria

Patients presenting for elective surgery who are either chronically on treatment-dose enoxaparin or who are being bridged with treatment-dose enoxaparin from another anticoagulant will be potentially recruited for this investigation.

- **Inclusion Criteria**
  Eligible patients need to be on treatment dose (1mg/kg twice daily or 1.5mg/kg daily) enoxaparin at the time of presentation for elective surgery and must be able to accurately report the timing of their last dose and the administered dosage. Patients must also be between the ages of 18-100 years of age and must be able to give written consent to participate. Patients who are bridged with enoxaparin from one of the currently available oral Anti-Xa inhibitors (Abixaban [Eliquis], Edoxaban [Sayvasa], and Rivaroxaban [Xarelto]) will be eligible as long as the duration from their last oral Anti-Xa inhibitor dose to their date of surgery is at least 5 days (120-hours).
- **Exclusion Criteria**
  Patients with severe renal insufficiency (creatinine clearance <30ml/min) will be excluded from the study, as the elimination of enoxaparin is known to be affected in this patient population. Pregnant patients will also be excluded, as the elimination and metabolism of enoxaparin is known to be altered in this patient population, and dose adjustments are recommended if treatment dose enoxaparin is used during pregnancy. Patients who are receiving enoxaparin as a bridge from another intravenous anti-Xa inhibiting medication will be excluded as this could unpredictably affect the results of anti-Xa testing. These medications include: Fondaparinux. Patients who are on an oral Anti-Xa inhibitor (Abixaban [Eliquis], Edoxaban [Sayvasa], and Rivaroxaban [Xarelto]) will be excluded if the duration of time from their last dose to the date of surgery (i.e., the duration that they are bridged with enoxaparin) is less than 5 full days (120 hours). .
- **Sample Size**
  Historical data from a previous publication (which showed that at 24-hours 58% of patients had an anti-Xa level ≥ 0.2IU/mL) was used to conduct a power analysis. In this prior study, data points were collected between 23.25-hours and 32-hours, and anti-Xa levels ranged between 0 and 0.54IU/mL. Assuming a similar relationship between anti-Xa activity levels and time observed in the original study pertains to later times, simulations using a sample size of 150 patients resulted in a threshold of approximately 29-hours with 95% confidence limits of approximately 28-hours and 33-hours. It was felt that a 5-hour window of the 95% confidence limit would provide acceptable guidance for clinical care. We expect some drop out and patient loss since some patients may have their surgical procedure cancelled following enrollment/randomization. In addition, occasionally the decision regarding the use of bridging therapy changes following a patient's visit to the preoperative assessment clinic. Therefore, we plan to enroll upwards of 180 patients until 150 patients have completed the study and have their data available for analysis.

Interventions and Interactions

- Patients on treatment dose enoxaparin will be identified at the time of their preoperative anesthesia consultation. These patients will be seen in the preoperative assessment clinic by a study team member and the study will be discussed with them at that time.
- Patients may elect to consent during their preoperative anesthesia consultation visit, or if they would like to think it over and talk with family/friends, a study team member will follow-up with them by phone to answer further questions.
- After consenting to the study, patients will be randomized to one of two groups.
  - Group one will be instructed to administer their last dose of enoxaparin at 07:00 in the morning on the day prior to their scheduled surgery date. This will mean

that patients who have their surgery scheduled for 07:00 the following day will be 24-hours removed from their last dose. Patients presenting for surgery later in the day would be slightly farther removed from their last dose, however this is currently considered normal clinical practice.

- Group 2 will be instructed to administer their last dose of enoxaparin at 19:00 in the evening two days prior to their scheduled surgery date. Patients presenting for surgery at 07:00 two days later will be 36-hours removed from their last dose. Patients presenting for surgery later in the day would be slightly farther removed from their last dose, but again this mimics normal clinical practice in which the timing of the last dose of self-administered enoxaparin is not routinely adjusted based on the scheduled surgical start time.

- All patients consented for the study will be called by a study team member or study coordinator two days before their surgical date to ensure they understand when they are supposed to self-administer their last dose of enoxaparin.
- Upon arrival for surgery, all consented patients will have demographic information recorded (age, weight, gender) as well as the enoxaparin dosage and the timing of their last administration.
- All patients in the study will have a blood sample drawn. Two laboratory tests will be sent.
  1). Anti-Xa level assay (Heparin Assay)
  2). Basic Metabolic Panel (BMP) (for evaluation of creatinine).
- When feasible, blood sampling will be performed at the same time that intravenous access for fluid/medication administration is obtained to minimize patient discomfort.
- Anti-Xa level testing will be performed using a chromogenic assay and a hybrid heparin/enoxaparin curve (Biophen Heparin 6 kit).
- The results of both of these tests will be collected from the electronic medical record after the results are posted.
- Following collection of the blood samples, the patient's participation in the study will be concluded.
- The results of the anti-Xa level test will be shared with the patient and the risk-benefit decision of proceeding with neuraxial block (if indicated) will be left to the anesthesiologist of record.

Outcome Measure(s)

The primary outcome of the study is the measurement of anti-Xa activity levels following the last treatment dose of enoxaparin in patients presenting for elective surgery. Anti-Xa level activity will be measured using a chromogenic assay and a hybrid curve calibrated to both heparin and enoxaparin. The randomization of patients to either the 24-hour group or the 36-hour group will allow for modeling, which will generate a prediction of the time point at which the level of anti-Xa activity can reliably be assumed to be lower than 0.2IU/mL.

Secondary outcomes will include determining the relationship of anti-Xa level activity over time (by using curve fitting or best-fit function) as well as attempting to determine if there are any patient conditions or characteristics that can predict delayed clearance of enoxaparin (elevated anti-Xa levels).

Analytical Plan

For the primary analysis, logistic regression of success criterion (anti-Xa activity level < 0.2 IU/mL) and 95% confidence limits at a success level (<0.2) of 95% likelihood will be utilized. For secondary analyses we plan to describe the best-fit function for anti-Xa activity levels over time. We also plan to explore clinical predictors for any anti-Xa activity levels > 1 standard deviation over the mean from the above function.

Human Subjects Protection

Subject Recruitment Methods

Patients on treatment dose enoxaparin will be identified at the time of their preoperative anesthesia consultation. These patients will be seen in the preoperative assessment clinic by a study team member and the study will be discussed with them. They will be given information related to the study (consent form). Patients may elect to consent to participation that day, or a study team member will follow-up with them by phone two days before their surgery to answer questions. If they choose to participate at that time the consent paperwork will be completed the day of surgery, but they will be randomized and instructed on when to self-administer their last treatment dose of enoxaparin prior to surgery.

Informed Consent

Signed informed consent will be obtained from each subject. Only providers listed as a primary or co-investigator, study team member or study coordinator will obtain written informed consent.

Confidentiality and Privacy

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a linkage file, store separately from the data. The linkage file will be kept secure, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed 3 years after closure of the study by shredding the documentation, consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Data and Safety Monitoring

The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff.

The cost of both laboratory tests (anti-Xa level and BMP) will not be billed to the patient. These costs will be covered by the study sponsor (Department of Anesthesiology).

Reporting of Unanticipated Problems, Adverse Events or Deviations

Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the principal investigator or designated member of the research team to the IRB and sponsor or appropriate government agency if appropriate.

References

1. Horlocker T, et al. Regional Anesthesia in the Patient Receiving Antithrombotic or Thrombolytic Therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition). Reg Anesth Pain Med 2010; 35:64-101.

2. Gulur P, Tsui B, Pathak R, Koury M, Lee H. Restrospective analysis of the incidence of epidural haematoma in patients with epidural catheters and abnormal coagulation parameters. Br J of Anaesth 2015; 114 (5): 808-11.

Appendix

1. Data collection form
2. Consent form