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1. Background

Over the past 20 years, there has been a dramatic increase in the rates of obesity in the United States. The US National Institutes of Health defines obesity as a body mass index (BMI) of ≥30-39.9 kg/m^2 and morbid obesity as a BMI of ≥ 40 kg/m^2, using height and weight to obtain BMI. According to data published by the US Department of Health and Human Services, over 35 percent of Americans were considered obese in 2009-2010.[1] Obese patients are at increased risk for cardiovascular and venous thromboembolic events due to associated comorbidities including hyperlipidemia, glucose intolerance, hypertension, and a sedentary lifestyle.[2] Treatment of cardiovascular and venous thromboembolic events often includes anticoagulation with low molecular weight heparin. Thus, there are a significant number of obese patients that will need therapeutic anticoagulation.

Landmark clinical trials that led to the approval of the low molecular weight heparin, enoxaparin, for treatment of venous thromboembolism and acute coronary syndromes did not list obesity as an exclusion criterion, but little data is available on the outcomes in this population due to underrepresentation in those trials.[3] Data on the safety and efficacy of enoxaparin in the obese population is derived mainly from observational or pharmacokinetic studies.[4] The implications of limited data can be very serious since appropriate dosing is crucial to ensure efficacy and to prevent adverse events including bleeding complications.

After low molecular weight heparin is administered, it predominantly concentrates in the plasma and highly vascular tissues with little distribution into fat tissue. Since dosing is based on weight, obese patients may receive higher doses; however, because there is low distribution into fat tissue this may result in elevated anti-Xa levels and thus they can be easily overdosed. It has been shown that anti-Xa activity is increased appropriately when the drug is administered to patients based on total body weight up to 144 kg.[5] The American College of Chest Physicians Evidence-based clinical practice guidelines recommend monitoring of anti-Xa levels in obese patients.[6] Enoxaparin has both anti-Xa and anti-IIa activity however, because of the higher anti-Xa:IIa ratio, anti-Xa levels are used as a marker of activity.[7] It has been suggested that the incidence of bleeding is increased when anti-Xa levels are elevated; however, data are conflicting.[6]

There is limited data available to guide dosing of patients above 150 kg. The largest prefilled syringe is 150 mg and has resulted in many clinicians capping the dose at 150 mg.[4] A pharmacokinetic study in 48 healthy obese volunteers (BMI 30-40 kg/m^2) at a single study center showed that dosing based on total body weight achieved similar maximum anti-Xa levels in both obese and non-obese patients, 1.563 IU/ml and 1.488 IU/ml respectively. The authors recommended no need to modify dosing in obese patients; however, this trial used 1.5 mg/kg daily, included healthy volunteers, and the highest weight studied was only 144 kg.[5] A prospective study in hospitalized patients with a BMI>30 kg/m^2 evaluated anti-Xa levels using 1 mg/kg twice daily.[8] Forty five percent of patients achieved a therapeutic anti-Xa level with the mean being 1.17 IU/ml. There was no difference in anti-Xa levels between those with and without bleeding episodes. The authors concluded no dose adjustment necessary in this study. The results from the above studies suggest standard dosing produces similar ant-Xa levels in non-obese and obese patients above 30 kg/m^2.

A retrospective study evaluating the dosing of enoxaparin in 26 morbidly obese hospitalized patients (BMI ≥40 kg/m^2) also evaluated anti-Xa levels.[9] A median dose of 0.8 mg/kg based on total body weight was utilized with maximum doses up to 150 mg. Forty six percent of patients achieved a goal anti-Xa level and 38% of patients were above the anti-Xa goal. The weight cut-off of 150 kg did not result in statistically significant differences in mean anti-Xa levels (1.12 IU/ml in patients over 150 kg vs 0.81 IU/ml in patients over 150 kg, p>0.05). Even though 4 out

of 10 patients with a supratherapeutic anti-Xa level experienced more bleeding events, these patients were noted to have additional risk factors for bleeding. This trial suggests that lower initial dosing of enoxaparin could be utilized in the morbidly obese population since the majority of anti-Xa levels were at or above goal.

There are a few studies looking at clinical outcomes that may be influenced by the dosing dilemma of enoxaparin in obesity. A subgroup analysis of the SYNERGY trial evaluated if BMI affected outcomes in hospitalized NSTEMI patients.[10] Patients at both extremes of weight were dosed with enoxaparin 1mg/kg based on total body weight with no capping of doses. Major bleeding, using the TIMI definition, during hospitalization was lower for patients with a BMI above 35 compared to those with a BMI below 20 (8.8% vs. 11.4%). In addition, obesity did not have an effect on the efficacy outcomes of mortality or myocardial infarction at 30 days and 6 months which led authors to conclude those with normal renal function should be dosed with 1 mg/kg of actual body weight regardless of body weight. However, only 3.5% of patients had a BMI>40 kg/m^2, thus, more research in that group was recommended. A meta-analysis that included hospitalized NSTEMI patients with a BMI>30 kg/m^2 also showed no increase in major bleeding in obese patients who were dosed based on total body weight.[11] In contrast, an observational study using the CRUSADE database of hospitalized NSTEMI patients showed an increased incidence of non CABG related bleeding in patients weighing >150kg receiving standard 0.95-1.05 mg/kg dosing compared to those receiving a lower initial dose of <0.95 mg/kg (11.4% vs. 6.5%, OR 2.42).[3] However, as seen in the previous studies, patients over 150 kg represented a small portion of the study population (0.92%) therefore more safety data is warranted in that group.

The Chest guidelines have recommended a dosing nomogram to adjust low molecular weight heparin doses; however, the study used to validate the nomogram was performed in a pediatric patient population.[12] Even though guidelines suggest monitoring and adjusting doses based on anti-Xa levels, little guidance is given on whether the initial dose should be empirically decreased to a more conservative dose. One strategy is to start with a lower dose, 0.8 mg/kg, which was the average dose used in the retrospective study performed by Deal et al. This study supports starting with a more conservative initial dose since 84% of patients were at or above the anti-Xa goal.[9]

Grady Health System is an inner city public hospital that serves a predominantly indigent patient population and includes a significant number of obese patients. Patients admitted to the hospital for anticoagulation treatment receive enoxaparin dosed 1 mg/kg twice daily using total body weight. Because of the significant obese patient population, clinical pharmacists often assist with dosing and monitoring in obese patients, including patients weighing more than 150 kg. Currently, there is no standard enoxaparin monitoring protocol and thus anti-Xa levels are ordered at the discretion of the physician or per the recommendation of a clinical pharmacist. Because of the ever increasing body habitus of the US patient population, there is a great need to determine optimal dosing regimens for obese patients in order to ensure therapeutic anti-Xa levels and prevent bleeding complications. Since previous studies have shown similar anti-Xa levels in patients with a BMI of 30-40 kg/m^2 and no increase in bleeding events, this study will investigate dosing in an underrepresented population of patients with a BMI >40 kg/m^2.[5,11] Using the higher BMI cut-off will also allow for more patients with a weight above 150 kg which was also underrepresented in the trials.

The purpose of this study is to determine an effective enoxaparin dosing strategy in medically ill, morbidly obese patients to achieve therapeutic anti-Xa levels. If an optimal regimen is discovered the ultimate goal will be designing a dosing and monitoring protocol.

2. Design
    a. Sample
        i. Inclusion
            1. Treatment dosing of enoxaparin (twice daily)
            2. BMI $\geq$ 40 kg/m^2
        ii. Exclusion
            1. <18 years of age
            2. Renal dysfunction (CrCl <30 ml/min) at any point during hospitalization while on enoxaparin
            3. Pregnancy
            4. Prisoners
            5. Active bleeding
            6. Already started on therapeutic enoxaparin and received >3 consecutive doses
            7. Therapeutic enoxaparin use within the last 3 months for >5 consecutive days
    b. Setting
        i. The location of study and data collection will take place in Grady hospital
    c. Recruitment
        i. Inpatients initiated on enoxaparin treatment doses will be prospectively identified using a Pharmacy Report to query medication orders in the electronic medical record system.
        ii. Consent will occur in patient's hospital room once the medical team is notified of patient eligibility
        iii. Allowing 3 doses to be given prior to inclusion in the study will allow for equitable recruitment since clinical pharmacists may not be available during the evening hours to assist with initial dosing and recruitment
    d. Procedures
        i. Eligible patients will be approached while inpatient for written consent
        ii. Patients will be randomized in a 1:1 fashion into the 0.8mg/kg or 1 mg/kg group (using total body weight) stratified by BMI
            1. Doses will be rounded to the nearest 10mg due to graduations on syringe
        iii. Initial anti-Xa levels
            1. Order levels 4 hours after at least three consecutive study doses of enoxaparin (will allow levels drawn between 3-5 hrs[6,8,9]). If the level is not drawn, it will be reordered after the next dose.
            2. Therapeutic anti-Xa: 0.5-1.1 IU/ml (GHS therapeutic range)
            3. Adjustments will be made according to the dosing nomogram until a therapeutic level is obtained (see appendix[12]). If a bleeding event occurs an anti-Xa level will be obtained.
        iv. Data Collection
            1. Baseline Data
                a. TBW, height, BMI
                b. BMI= TBW(kg)/height (m)^2
                c. Age, Sex, Race
                d. Scr, CrCl (Cockcroft-Gault equation)
                e. Indication for treatment
            2. Post intervention
                a. Scr, CrCl

b. Initial dose of enoxaparin (mg/kg and mg)
c. Initial anti-Xa level and timing of level
d. Number of hours post dose
    i. Level at 4 hours
    ii. Level within range of 3-5 hours
e. Total number of doses received prior to level

3. Subsequent doses of enoxaparin (mg/kg and mg)
4. Subsequent anti-Xa levels after dosing adjustments
5. Time to first therapeutic anti-Xa level
6. Total days on enoxaparin
7. Bleeding events
    a. Decrease in Hgb
    b. Site of bleed
    c. Blood product use
    d. INR at onset of bleeding event for patients on warfarin
    e. Additional anticoagulants and antiplatelets (date initiated and dose)
    f. Platelet count at onset of bleeding event
    g. Anti-Xa level at onset of bleeding event
    h. PT and/or aPTT if available

v. Respondent Burden-Total respondent burden will be minimal and depend on the time it takes to consent. Laboratory work would have to be done for this medication regardless of whether they were in the study or not.

e. Study Objectives/Outcomes

i. Primary Objective
1. To determine if enoxaparin dosing using 0.8mg/kg is more effective for achieving therapeutic steady state anti-Xa levels in morbidly obese patients when compared to 1 mg/kg dosing. (Morbid obesity is defined as a BMI > 40 kg/m^2)

ii. Secondary Objectives
1. To compare time to therapeutic anti-Xa levels for both dosing regimens
2. To compare anti-Xa levels for both dosing regimens
3. To compare number of dose adjustments required to achieve therapeutic anti-Xa levels using a dosing nomogram
4. To validate dosing nomogram used to adjust low molecular weight heparin doses
5. To evaluate major and minor bleeding events

iii. Primary Outcome
1. Proportion of patients with an initial therapeutic anti-Xa level at steady state in each group
    a. Peak anti-Xa drawn 3-5 hours post dose after receiving at least 3 consecutive doses

iv. Secondary Outcomes
1. Time to therapeutic anti-Xa level for both groups
2. Mean/Median therapeutic anti-Xa level for both groups
3. Mean/Median number of dose adjustments required to achieve therapeutic anti-Xa level for both groups
4. Proportion of patients with major and minor bleeding events (will follow until anti-Xa level is therapeutic)

a. Major bleed: Hgb drop of ≥2g/dL, transfusion of 2 or more units of blood products, or retroperitoneal, intraocular, or intracranial hemorrhage[13]
b. Minor bleed: bleeding events not meeting major bleed criteria

f. Risks to participation
    i. Patients started on enoxaparin will be at risk for bleeding complications which is a known risk for this medication. Risk will be reduced by obtaining anti-Xa levels and adjusting the dose as needed. Other possible risks may be , anemia, decrease in platelets, elevation of liver enzymes, diarrhea, and nausea
g. Benefits to subject or future benefits
    i. By completing this study a strategy for dosing enoxaparin may be established for obese patients that is safer and allows for quicker therapeutic levels.
h. Data analysis
    i. Sample Size- In order to detect a 15% difference in the primary endpoint with a 2-sided significance level of 0.05, 50 patients per dosing group is needed to provide 80% power.
    ii. Statistical Analysis
        1. Descriptive statistics will be used for all variables. Primary outcome will be analyzed using chi-square. Time to event will be analyzed using survival curves and log rank test. Medians will be compared using wilcoxan rank test.

3. Training
CITI training will be completed by all personnel. Training on explaining risks and benefits during consent process and on using dosing nomogram will be done prior to initiation of study.

4. Plans for data management and monitoring
Safety data will be collected as mentioned above to monitor for adverse drug reactions, specifically bleeding. Patients with a decline in renal function that prompts a dose change will be excluded so that they may be put on a reduced dose listed in medication package insert.

5. Confidentiality
The data will be identifiable upon collection and will be kept on a password protected file on a computer in a locked office. The data will be de-identified after data analysis and only the study personnel will have access to the code that links identifiers to subjects.

6. Informed Consent
Informed written consent will be obtained in person while the patient is hospitalized.

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Appendix A. Dosing Nomogram for Adjusting Enoxaparin[14]

Anti-factor Xa level (IU/mL)	Hold Next Dose	Dose Change	Repeat Anti-Factor Xa*
<0.35	No	Increase by 25%	4h after next dose
0.35-0.49	No	Increase by 10%	4h after next dose
0.5-1.1	No	No	---
1.2-1.5	No	Decrease by 20%	4h after next dose
1.6-2.0	No	Decrease by 30%	4h after next dose
>2.0	Until level is 0.5 IU/mL	Decrease by 40%	4h after next dose

Adapted from CHEST 2001 and adjusted per institutional procedures
*Will obtain level if CrCl<30 ml/min or bleeding event