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Evaluation of Unfractionated Heparin Dosing for Thromboprophylaxis using Anti-Xa Levels in Obese Critically Ill Patients: A Retrospective Study

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Abstract

Purpose: This study aims to evaluate whether current dosing recommendations of UFH for the prevention of thromboembolism is appropriate in obese critically ill patients utilizing Anti-Xa levels.

Materials and methods: A pilot, observational and retrospective chart review of critically ill patients was evaluated. Patients aged ≥ 18 years were included if they received subcutaneous UFH for thromboprophylaxis and had a recorded Anti-Xa level taken four to five h after the administration of UFH. Identified patients were categorized into two groups: BMI < 30 kg/m² or BMI ≥ 30 kg/m². Anti-Xa heparin activity levels were then compared. Statistical analysis was performed using Student's t-test.

Results: A total of 130 adult ICU patients were included in this study. For all critically ill patients receiving 5,000 units of subcutaneous heparin every 8 h, there was no statistically significant difference in Anti-Xa levels between the groups ($p=0.287$). There was no incidence of DVT/ PE reported from either group.

Conclusion: This study suggests that there is no significant difference in Anti-Xa levels between obese critically ill patients and non-obese patients receiving traditional UFH dosing for thromboprophylaxis.

Keywords: Low molecular weight heparin; Anticoagulation; Anti-Factor Xa activity; Monitoring; Dosing; Obesity

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Introduction

Venous thromboembolism (VTE), a spectrum of diseases including deep venous thrombosis (DVT) and pulmonary embolism (PE), frequently affect hospitalized patients and is associated with significant morbidity and mortality [1]. Critically ill patients requiring admission into the Medical and Surgical Intensive Care Units (MICU and SICU) have at least one risk factor for VTE that may persist for several weeks after discharge [2,3]. The incidence of pulmonary embolism (PE) in the United States is estimated to be 1 in 1000 patients per year, accounting for 200,000 to 300,000 hospitalizations annually [4,5]. Studies suggest between 5-10% of all in-hospital deaths occurred due to PE [6-8].

Although sequential compression devices (SCDs) are routinely

used in hospitalized patients, the American College of Physicians (ACP) guidelines published in 2011 recommend additional chemical prophylaxis with unfractionated heparin or another chemical anticoagulative agent in patients as a first-line thromboprophylaxis therapy, unless the assessed risk for bleeding outweighs the likely benefits [2]. The American College of Chest Physicians and American Academy of Family Physicians

(AAFP) recommend 5,000 units of fixed low-dose unfractionated heparin (UFH) every 8 to 12 h for adult DVT prophylaxis [9].

The effectiveness of traditional UFH dosing for thromboprophylaxis has been often evaluated based on patients' clinical outcomes such as the incidence of DVT, PE, major bleeding and death. Limited data are available on the effectiveness on the correlation between UFH dosing and laboratory values (such as Anti-Xa levels) as well as its effectiveness in preventing thromboembolic events among obese, critically ill patients. The suggested fixed UFH dosing of 5,000 units every 8 to 12 h subcutaneously may be suboptimal in this patient subgroup as heparin pharmacokinetics depends on a number of patient variables, including thickness of the adipose tissue layer [10]. Monitoring Anti-Xa levels may provide more appropriate therapeutic goal of heparin thromboprophylaxis, especially in severe obesity, in unexpected bleeding complications secondary to anticoagulation with use of UFH, in renal failure, and in pregnant patients in whom UFH are used for treatment or prevention of thrombosis [11,12].

The purpose of this study is to evaluate whether current dosing recommendations of UFH for the prevention of thromboembolism is appropriate in the obese critically ill patient population utilizing Anti-Xa levels. Appropriate empiric dosing adjustments for obese population and establishment of suggestive Anti-Xa level range would yield potential improvements in outcomes in preventing incidences of thromboembolism in the intensive care unit.

Methods

Study population

Male and female patients in the Surgical Intensive Care Unit (SICU) and Medical Intensive Care Unit (MICU) at Long Island Jewish Medical Center, N.Y. who are at least 18 years of age were included in the study if they had received at least three doses of subcutaneous UFH for thromboprophylaxis and had a recorded Anti-Xa level taken four to five hours after the administration of UFH. Patients without documented demographic information (age, weight, height or serum creatinine level), recorded Anti-Xa level taken four to five hours after the third dosing of UFH administration, receiving heparin infusions, other anti-coagulants or mechanical thromboprophylaxis were excluded. Informed consent was not obtained as the study was a retrospective, observational chart review.

Study design

This study was a pilot, observational, retrospective chart review evaluating the effectiveness of the recommended dosing of subcutaneous unfractionated heparin for thromboprophylaxis using Anti-Xa levels in critically ill obese and non-obese patients. The protocol was approved by the North Shore-Long Island Jewish Health System Institutional Review Board. The data were collected and evaluated from a list generated by Sunrise Clinical Manager or pharmacy monitoring forms of patients who have received subcutaneous UFH for VTE prophylaxis while in the surgical or medical intensive care units from January 2012 through December 2012. After eligible patients were identified,

patients were divided into two groups: Those with BMI < 30 kg/m² and those with BMI ≥ 30 kg/m². For each group, the following information was recorded on the data collection sheet for evaluation: age, weight, height, ideal body weight (IBW), UFH dose used, Anti-Xa levels, and serum creatinine (SCr) drawn on the same day as Anti-Xa levels were drawn. The primary efficacy endpoint was anti-Xa heparin activity levels of 0.11-0.25 IU/mL. The incidence of deep venous thromboembolism (DVT) or pulmonary embolism (PE) from either group was reviewed as a secondary endpoint. Creatinine clearance (CrCl) was calculated using the Cockcroft and Gault equation. Mann-Whitney was conducted to test the statistically significant difference between the Anti-Xa levels of the two groups.

To protect against and/or minimize any potential risks to confidentiality, all information was de-identified by using only the initial of the patient's name so that individual subjects cannot be recognized and the information will no longer be considered Protected Health Information (PHI). All patient specific health information was kept confidential by developing a coded chart datasheet. All data were stored in a password protected computer database that can only be accessed by the investigators to maintain patient confidentiality.

Statistical Analysis

We estimated that with 75 patients in each group, the study would have 90% power to show a 10% change, at a two-sided alpha level of 0.05. Assuming that we would not be able to evaluate data from 5% of the patient, we estimated that we would have to enroll at least 100 patients.

The primary population for the efficacy analyses comprised all patients who were identified to be included in the study. For continuous variables we used Mann-Whitney to compare between obese (BMI ≥ 30 kg/m²) and non-obese groups (BMI < 30 kg/m²) and for categorical variables we used Fisher's Exact Test. The incidence of thromboembolic events was defined as the clinical outcomes and compared in two study groups. All analyses were performed with the SAS software package, version 9.2 (SAS Institute Inc. 100 SAS Campus Drive Cary, NC 27513-2414, USA). This study was approved by the Hofstra North Shore-LIJ Institutional Approval Board number IRB# 12-314B.

Results

Patients

After assessments for eligibility, a total of 130 SICU and MICU patients were identified and included in the study for evaluation (non-obese patients: n=71; obese patients: n=59). **Table 1** shows the baseline characteristics of the two groups. The mean (± SD) age was 72.45 ± 15.8 years and 61.29 ± 16.08 years in non-obese and obese patient groups, respectively. For the non-obese patient group, the median SCr (Q1-Q3), and median CrCl (Q1-Q3) were 0.92 (0.68-1.95) mg/dL and 41.64 (24.96-73.77) ml/min, respectively. For the obese patient group, the median SCr (Q1-Q3), and median CrCl (Q1-Q3) were 1.22 (0.8-2.3) mg/dL, 54.8 (34.8-88.42) ml/min, respectively. This is listed in **Table 1**.

Efficacy outcomes

The median (Q1-Q2) Anti-Xa heparin activity level was 0.11 (0.08-0.15) IU/ml in non-obese group and 0.10 (0.08-0.12) IU/ml in obese group (**Table 2**). There was no statistically significant difference in anti-Xa heparin activity levels between the two groups ($p=0.1785$). This is listed in **Table 2**. Also, there was no clinically significant difference between the groups as there was no incidence of thromboembolic events (DVT or PE) reported from either group. Therefore, higher doses of UFH may not be required for critically ill obese patients.

Discussion and Conclusion

Obesity remains a significant risk factor for the development of thromboembolism in the critically ill patient population [13]. The ACCP practice guidelines suggest increasing the dose of chemical thromboprophylaxis agent for the prevention of VTE in obese patients [14]; however, recommendations for VTE prophylaxis in obese patients are not clear as limited prospective trials have been conducted in this patient subset of the population [3]. Given the alarming rise in the prevalence of obesity in our country, an understanding of optimal UFH dosing regimen in prevention of VTE is crucial.

Current practice of administering fixed subcutaneous heparin dosing every 8 to 12 h may be suboptimal among patients given that the pharmacokinetics of heparin depends on several patient variables, including the thickness of the adipose tissue layer [10]. While UFH is one of the most frequently used thromboprophylaxis in intensive care units, there is no defined therapeutic range for Anti-Xa level for this purpose. Previous study, however, had suggested that therapeutic anti-Xa levels obtained approximately 4 to 5 h after the third or fourth subcutaneous dose of UFH at 0.11-0.25 U/mL may be effective for thromboprophylaxis [10].

Our study attempted to correlate the current UFH dosing regimen (5,000 units given subcutaneously every 8 hours) with Anti-Xa levels drawn after the third dose. In our study, we found no statistically significant difference in Anti-Xa levels between the 2 groups. In fact, following the third dose of subcutaneous unfractionated heparin, both groups were able to achieve the desired anti-Xa level that previous studies had suggested as optimal for thromboprophylaxis. As we had only drawn one anti-Xa level per patient, it remains unclear if these patients were able to maintain their anti-Xa level at the desired range of 0.11-0.25 IU/ml throughout their entire hospital stay. Future studies may be warranted to look at trend in anti-Xa levels with this fixed dosing regimen.

There was no symptomatic VTE (DVT and PE), bleeding events, or heparin induced thrombocytopenia (HIT) in both group. No adverse events occurred in the population studied.

The limitations of our study include the small sample size and the lack of any significant clinical events. A larger, multi-center, randomized trial is obviously needed to firmly establish the correlation between UFH dosing regimen and Anti-Xa levels as well as its effectiveness as chemical thromboprophylactic agent among obese medical and surgical patients. Nevertheless, our study demonstrate that a fixed UFH dosing regimen at the current recommended 5,000 unit every 8 to 12 h may be appropriate for obese patients. Furthermore, there was no VTE events observed in either group.

In conclusion, these data demonstrate that a fixed UFH dosing regimen is effective in achieving therapeutic anti-Xa levels in non-obese and obese patient populations alike.

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Table 1 Demographic data.

Parameter	Non-obese (BMI<30 kg/m ²)	Obese (BMI ≥ 30 kg/m ²)	P value
Number of Patient	71	59	
Sex, Female n (%)	34 (43.59%)	23 (46%)	0.279
Age, years mean ± SD	72.45 ± 15.83	61.29 ± 16.08	0.0009
18-45, years n (%)	8 (10.26)	9 (18)	
46-55, years n (%)	6 (7.69)	8 (16)	
56-65, years n (%)	9 (11.54)	12 (24)	
>65, years n (%)	55 (70.51)	21 (42)	
Serum Creatinine, mg/dL median (Q ₁ -Q ₃)	0.92 (0.68-1.95)	1.22 (0.8-2.3)	0.082
Creatinine clearance*, ml/min median (Q ₁ -Q ₃)	41.64 (24.96-73.77)	54.8 (34.8-88.42)	0.076

BMI: Body Mass Index; N: Number of Patient; SD: Standard Deviation; Q₁: Lower Quartile; Q₃: Upper Quartile. *Creatinine clearance was calculated using Adjusted Body Weight (ABW)

Table 2 Efficacy outcomes.

Parameter	Non-obese BMI<30 kg/m ²	Obese BMI ≥ 30 kg/m ²	Mann-Whitney Test (p)
Number of Patient	71	59	
Anti-Factor Xa activity, IU/ml median (Q ₁ -Q ₃)	0.11 (0.08-0.15)	0.10 (0.08-0.12)	0.179

BMI: Body Mass Index; Q₁: Lower Quartile; Q₃: Upper Quartile

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