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Unfractionated heparin dosing for therapeutic anticoagulation in critically ill obese adults ☆

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ABSTRACT

Purpose: Research evaluating unfractionated heparin (UFH) dosing in obese critically ill populations is limited. This study aimed to determine optimal weight-based and total therapeutic infusion rates of UFH in this population.
Methods: This retrospective cohort study compared adults on UFH infusions in intensive care units from May 2011 through October 2013 across 3 weight strata: 95 to 104 kg (control), 105 to 129 kg (high weight), and greater than or equal to 130 kg (higher weight). Primary outcomes included total and weight-based infusion rates for therapeutic anticoagulation.
Results: To achieve therapeutic activated partial thromboplastin times, higher weight patients had higher mean infusion rates compared with control (2017 vs 1582 U/h; $P = .002$). Mean weight-based therapeutic infusion rate was lower in the higher weight group compared with control (13.1 vs 15.8 U kg^{-1} h^{-1}; $P = .008$). Post hoc analyses indicated mean weight-based infusion rate to achieve therapeutic anticoagulation was 15 U kg^{-1} h^{-1} in patients less than 165 kg and 13 U kg^{-1} h^{-1} in patients greater than 165 kg.
Conclusions: Patients greater than or equal to 130 kg have lower weight-based heparin requirements compared with patients 95 to 104 kg. This difference appears to be driven by patients greater than 165 kg. Patients greater than 165 kg have lower weight-based heparin requirements, whereas patients from 105 to 164 kg have weight-based requirements similar to a normal-weight patient population. Initiating heparin at appropriate weight-based doses for obese patients may optimize anticoagulation.

1. Introduction

The prevalence of obesity in the United States continues to grow [1]. In 2009-2010, 35.7% of US adults were obese, defined as body mass index (BMI) greater than 30 kg/m^2. Although the prevalence of moderate obesity seems to have plateaued recently, the prevalence of severe/morbid obesity (BMI greater than 40 kg/m^2) continues to rise from 3.9% in 2000 to 6.6% in 2010 [2]. Optimal medication dosing in obese patients is challenging due to differences in pharmacokinetic parameters in obese patients.

For the treatment of venous thromboembolism (VTE), the dose of unfractionated heparin (UFH) recommended by current guidelines is an initial bolus dose of 80 U/kg followed by 18 U kg^{-1} h^{-1} as a continuous infusion [3]. A slightly lower bolus dose of 70 U/kg followed by 15 U kg^{-1} h^{-1} as a continuous infusion is recommended for patients with stroke or cardiac event as the indication for anticoagulation with UFH. Dosing strategies in the obese population are not addressed. Research supports UFH dosing based on actual body weight in nonobese patients; however, few patients in these studies were overweight or obese [4,5]. Use of actual body weight was found to be superior to either adjusted dosing weight or ideal body weight (IBW) in patients greater than 10 kg above IBW; however, the highest weight included in this investigation was 184 kg [5]. Additional proposed strategies for dosing in obese patients include use of actual body weight with dose caps or use of estimated blood volume [5,6]. Neither of these strategies has been shown to be consistently effective in the morbidly obese.

The goal of therapeutic anticoagulation with UFH is to achieve therapeutic activated partial thromboplastin time (aPTT) or anti-Xa levels within 24 hours to decrease the risk of recurrent thrombosis while minimizing bleeding risk [7]. Studies have demonstrated increased time to therapeutic anticoagulation in obese patients compared with nonobese patients, although results are inconsistent [8,9]. The clinical significance of this extended time to therapeutic anticoagulation in obese critically ill patients is unknown but could result from administration of inadequate bolus doses or initial infusion rates. Obese patients are also at an increased risk of thrombosis compared with the nonobese population [10].

Although there is documented difficulty in dosing heparin in obese patients, the literature does not provide definitive answers on the most appropriate management of these patients. Furthermore, critically ill obese patients are underrepresented in heparin literature, and thus,

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optimal dosing strategies for this population have not been established. The purpose of this study was to determine the appropriate weight-based and total therapeutic infusion rates of UFH for critically ill patients weighing greater than 105 kg.

2. Methods

This study was a retrospective cohort study, which included patients in adult intensive care units (ICUs) initiated on continuous infusion UFH for therapeutic anticoagulation at a 1059-bed academic medical center from May 1, 2011, through October 31, 2013, who weighed greater than or equal to 95 kg. The study was approved by the institutional review board with a waiver of consent. At our institution, prescribers may choose to initiate either prescriber- or nurse-managed heparin protocols. Therapeutic aPTT ranges are selected by prescribers as follows: standard (aPTT, 50-80 seconds), low (aPTT, 50-65 seconds), and high (aPTT, 65-80 seconds). Intravenous UFH boluses upon initiation of the infusion and with dose increases are optional based on prescriber preference. Both prescriber- and nurse-managed protocols with all 3 aPTT goal ranges were included. The standard and high nomograms at our institution recommend a flat bolus dose and initial infusion rate based on approximately 70 U/kg and 15 U kg^{-1} h^{-1}, respectively, for weight ranges in intervals of 10 kg [11]. The low nomogram recommends a flat bolus dose of approximately 60 U/kg followed by initial infusion rate of 12 U kg^{-1} h^{-1}. The boluses and initial infusion rates for standard and high nurse-managed nomograms are capped at 7700 U and 1650 U/h, respectively, for patients greater than or equal to 105 kg. Similarly, the low nurse-managed nomogram is capped at 6600 U and 1300 U/h for patients greater than or equal to 105 kg. In addition to our aPTT goal-directed nomograms, prescribers may also select indication specific nomograms for acute coronary syndrome (ACS) and neurointerventional postcoil, which have lower dose caps (maximum bolus 4000 U and initial infusion 1000 U/h). Indication specific nomograms using lower dose caps were excluded as the lower dose caps could have confounded results.

Additional exclusion criteria included dose-adjustments not based on aPTT, baseline aPTT greater than 50 seconds, goal other than therapeutic aPTT, tissue plasminogen activator administration for current event, intra-aortic balloon pump as indication for anticoagulation, ventricular assist device or extracorporeal membrane oxygenation, and age less than 18 years. Each patient was included once, and analysis was performed on first initiation of continuous infusion UFH during the study period. Individual exclusion criteria for specific analyses are included in Fig. 1.

The primary outcomes were the total and weight-based therapeutic infusion rates required to achieve therapeutic anticoagulation compared across 3 weight strata. "Therapeutic rate" was defined as the UFH infusion rate at the first of 2 consecutive aPTT values within ordered goal range. Predefined weight strata included a control group of patients 95 to 104 kg and 2 comparator groups of patients 105 to 129 kg (high weight group) and greater than or equal to 130 kg (higher weight group). The weight range of 95 to 104 kg was deemed appropriate for a control group because it included patients who received weight-based dosing using actual body weight and are below the dose capping from the nurse-managed nomograms. The decision to divide patients into weight-based groups of 105 to 129 kg and greater than or equal to 130 kg was made a priori and based on clinical experience of the investigators. All patients who achieved therapeutic aPTT were included in this analysis. Patients who had heparin discontinued before achieving a therapeutic aPTT were not included.

Secondary outcomes included the infusion rate required to achieve an aPTT greater than 50 seconds, time to therapeutic aPTT and time to aPTT greater than 50 seconds, and number of dose adjustments to achieve therapeutic aPTT compared across weight strata. "Infusion rate required for an aPTT greater than 50 seconds" was defined as the infusion rate at the time of the first of 2 consecutive aPTT values greater than 50 seconds. Because aPTT goals varied by patient, this parameter was evaluated to capture the rate required to cross the therapeutic threshold of an aPTT greater than 50 seconds. "Time to therapeutic aPTT" and "time to aPTT greater than 50 seconds" ("time to" analyses) were defined as the period from first documentation of UFH initiation

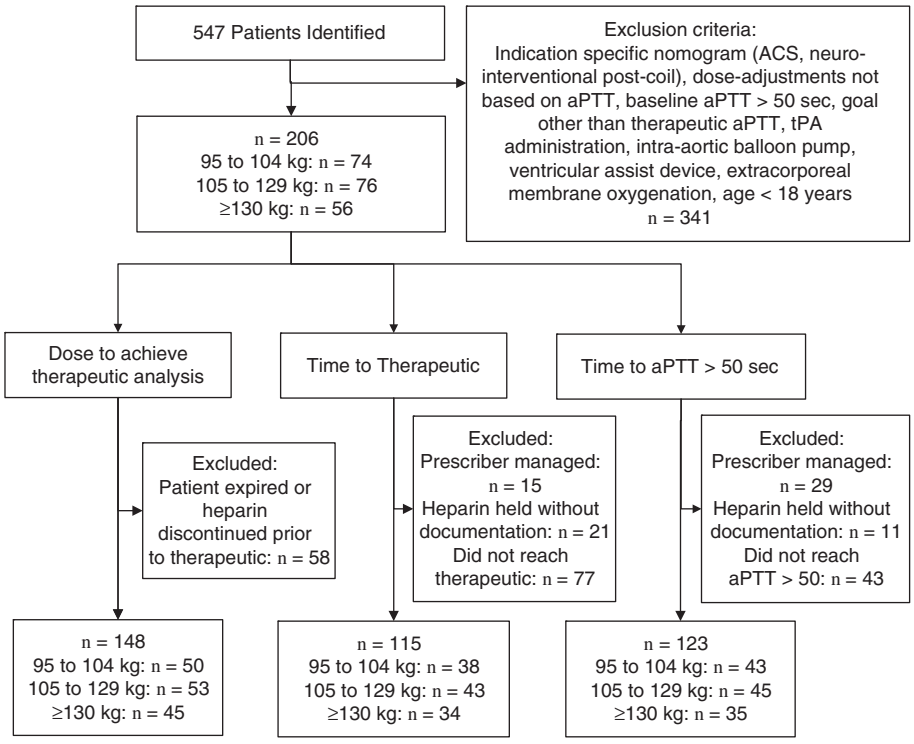

Fig. 1. Study patients.