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Abstract

Background: Despite large interpatient variability in dose response, heparin is utilized for treatment of venous thromboembolism (VTE). Current data on the optimal heparin dosing in obese patients are conflicting. **Objective:** The objective was to evaluate the time and dose required to achieve a therapeutic activated partial thromboplastin time (aPTT) in nonobese, obese, and severely obese patients using a pharmacist-directed heparin dosing protocol. **Methods:** This was a retrospective cohort study in a single center community hospital inpatient setting. Adult patients receiving heparin for VTE treatment from July 1, 2013, to July 31, 2015, were evaluated. Patients were categorized into 3 groups: nonobese (BMI < 30 kg/m2), obese (BMI = 30-39.9 kg/m2), and severely obese (BMI ≥ 40 kg/m2). Data on height, weight, initial bolus dose, initial infusion rate, time to therapeutic aPTT, and therapeutic infusion rate were collected. Dosing body weight (DBW) was utilized for patients 20% over their ideal body weight (IBW). The primary outcome was time to therapeutic aPTT. **Results:** Analysis included 298 patients. Median times to therapeutic aPTT (hours:minutes) in the nonobese, obese, and severely obese were 15:00 (interquartile range [IQR] = 8:05-23:21), 15:40 (IQR = 9:22-25:10), and 15:22 (IQR = 7.54- 23:40), respectively (P = 0.506). There was no difference in bleeding among the nonobese (14%), obese (13.9%), or severely obese groups (7.9%; P = 0.453). No adverse thrombotic events occurred during hospitalization. **Conclusion:** Using a DBW for heparin dosing in patients 20% over their IBW resulted in similar times to therapeutic aPTT and adverse events in the nonobese, obese, and severely obese.

Background

Venous thromboembolism (VTE), including deep-vein thrombosis (DVT) and pulmonary embolism (PE), occurs in 104 out of every 100 000 individuals with up to 4.8% and 7.7% developing recurrence or adverse bleeding events within 30 days.[1] The obese population is more likely to develop a VTE compared with the nonobese population.[2-4] The prevalence of

obesity (body mass index [BMI] ≥ 30 kg/m^2) in the United States continues to rise, with regional obesity ranging from 25.2% to 31.2% and the Midwest region having the second highest prevalence at 30.7%.[5] Intravenous heparin is frequently a drug of choice in hospitalized patients with VTE, but weight-based dosing is challenging in obese and severely obese patients because of the drug's unpredictable pharmacokinetic properties.

Heparin's distribution is limited primarily to blood volume. [6,7] Because of limited distribution into adipose tissue, dosing lower than institutional protocol has been observed in obese patients to avoid potential overdosing and subsequent adverse bleeding events.[8] Subjects included in early trials establishing weight-based heparin dosing for acute VTE had a mean weight of 80 kg, and these studies did not address dosing in the obese patient population.[9,10] More than 2 decades since those studies, the average weight of patients has increased, leaving the question of what weight is the most appropriate to use when dosing heparin for VTE treatment.[11]

Implementation of pharmacist-directed heparin therapy using standardized dosing protocols has been reported.[12,13] Pharmacist-directed heparin adjustments lead to an increased number of patients within therapeutic range compared with physician adjustments.[12] A pharmacist-directed heparin dosing protocol was implemented in our hospital in 2008 (Table 1). The protocol utilizes actual body weight (ABW) unless the patient is 20% over their ideal body weight (IBW), at which point a dosing body weight (DBW) is used. Ideal and DBW calculations are displayed in Table 2. Regardless of weight, the initial bolus dose and initial infusion rate are limited to 10 000 U and 2500 U/h, respectively. Serial activated partial thromboplastin time (aPTT) values are used to guide dosing, and dose titrations are made to achieve a therapeutic aPTT of 57 to 96 s, determined based on laboratory correlation to 0.3 to 0.7 U/mL by an anti-Xa activity assay. Multiple studies have demonstrated a lower risk of recurrent VTE when therapeutic aPTTs are achieved rapidly.[14,15] With obesity steadily rising in the United States, it is important to assess optimal drug dosing in this patient population. The objective of this study was to evaluate time to first therapeutic aPTT and doses required to achieve a therapeutic aPTT in nonobese, obese, and severely obese patients within our institution when a pharmacist-directed heparin dosing protocol was utilized.

Table 1. Pharmacy Dosing Protocol.

Initial Bolus	Bolus Cap	Initial Infusion Rate	Initial Infusion Cap	Goal aPTT
80 U/kg	10 000 U	18 U/kg/h	2500 U/h	57-96 sec

aPTT	Bolus Dose	Hold (minutes)	Rate Change	Repeat aPTT[a]
<45	60 U/kg	0	Increase by 4 U/kg/h	6 hours
45-56	40 U/kg	0	Increase by 2 U/kg/h	6 hours
57-96		Therapeutic range		Next AM labs[b]
97-115	0	0	Decrease by 1 U/kg/h	6 hours
116-150	0	30	Decrease by 2 U/kg/h	6 hours
151-163	0	60	Decrease by 3 U/kg/h	6 hours
>163	0	90	Decrease by 4 U/kg/h	6 hours

Abbreviation: aPTT, activated partial thromboplastin time.
[a]aPTT repeated 6 hours after dose change.
[b]aPTT will be repeated every 6 hours until 2 consecutive therapeutic range PTT results are measured; then, frequency will change to once daily with morning labs.

Table 2. Dosing Definitions.

IBW (kg)	• Males: 50 + (2.3 × Height in inches > 60 inches) • Females: 45.5 + (2.3 × Height in inches > 60 inches)
DBW (kg)	IBW + [0.4 (ABW − IBW)]

Abbreviations: ABW, actual body weight; DBW, dosing body weight; IBW, ideal body weight.

Materials and Methods

Study Design and Population

This was a retrospective, single-center cohort study. RxConsult, a proprietary heparin dosing and monitoring program within the institution, was utilized to identify patients 18 years or older who were receiving heparin for the indication of VTE treatment, including DVT or PE, and managed by the pharmacy dosing protocol from July 1, 2013, to July 31, 2015. Indication for heparin therapy was based on prescriber documentation in the consult to pharmacy for heparin dosing; therefore, if patients had both DVT and PE, it was not captured for the purposes of this evaluation. RxConsult is a computer program designed for our institution to assist with dosing and monitoring of patients receiving therapeutic heparin. When a new patient is initiated on heparin, a new patient-specific profile must be entered into RxConsult, including the patients' name, age, sex, height, weight, and indication. RxConsult will calculate the patient's IBW and determine if the patient's ABW is 20% over IBW to determine the correct bolus dose and infusion rate for the patient based on our dosing protocol. Each aPTT is entered into RxConsult, and the resultant rate change and/or bolus will be calculated by the program. Patients were excluded if they had a therapeutic aPTT obtained prior to steady state, which was defined as 6 hours from heparin initiation. RxConsult was used to extract base-line demographics and dosing information, including age, sex, height, ABW, indication, aPTT values, time to first therapeutic aPTT, and heparin information, which included initial bolus dose, initial infusion rate, therapeutic infusion rate, and duration of heparin therapy. Bleeding events and recurrent thrombotic events were identified from the physician discharge summary, and use of thrombolytic agents was identified via the electronic medical record. Thrombolytic agents included systemic alteplase 50 or 100 mg and catheter-directed tenecteplase 2.5, 5, or 10 mg.

Outcomes

The primary outcome was time to first therapeutic aPTT. A therapeutic aPTT was considered 57 to 96 s per institutional standards. Time to therapeutic aPTT was calculated in hours from the start of bolus dose to the first laboratory-reported therapeutic aPTT. Secondary outcomes included bleeding or thrombotic events while receiving heparin therapy and percentage of therapeutic aPTT values. Bleeding was defined as either a drop in hemoglobin from a baseline of ≥2 g/dL with subsequent transfusion of 2 or more units of packed red blood cells (PRBCs) while on heparin therapy or documented bleeding by the provider in the discharge summary.

Thrombotic events were defined as documentation of a thrombus in a new location and/or extension of current thrombus after initiation of heparin.

Data Analysis

Patients were categorized into 3 groups based on BMI: nonobese (BMI < 30 kg/m^2), obese (BMI = 30-39.9 kg/m^2), and severely obese (BMI $\geq$ 40 kg/m^2).16 Continuous data were described using means and SDs for variables considered to be normally distributed and medians and interquartile ranges (IQRs) for variables considered to be nonnormally distributed. Baseline demographics and clinical characteristics were compared between groups using analysis of variance, with Dunnett t-test for post hoc comparisons when needed. χ^2 Analyses and Kruskal-Wallis tests were used for nonparametric data. Patients with 3 or more consecutive therapeutic aPTTs, representing a minimum of 18 hours of a consistent infusion rate, were further analyzed to determine dose based on ABW, IBW, and DBW. Statistical analysis was conducted using Statistical Package for Social Sciences version 23.0 (SPSS v23.0). The study was approved by the institutional review board of the hospital.

Results

A total of 298 patients were eligible for study inclusion. Four patients were excluded for therapeutic aPTTs obtained prior to steady state, leaving a total of 294 patients for final analysis. Patient characteristics are dis- played in Table 3. Patients in the severely obese group (mean $\pm$ SD = 57.3 $\pm$ 15.6 years) were younger than those in the nonobese (66.2 $\pm$ 16.5 years, P < 0.001) and obese groups (65.8 $\pm$ 14.5, P = 0.001).

Table 3. Patient Characteristics.

	Nonobese (n = 121)	Obese (n = 110)	Severely Obese (n = 63)
Male, n (%)	62 (51.2)	54 (49.1)	27 (42.9)
Age (years)[a,b]	66.2 ± 16.5	65.8 ± 14.5	57.3 ± 15.6
ABW (kg)[a]	74.8 ± 15.9	98.2 ± 16.1	149.7 ± 43.5
ABW range (kg)	39.5-113.8	68-143.4	94.1-309.5
BMI (kg/m^2)	24.9 ± 3.5	33.9 ± 2.8	50.8 ± 11.5
BMI range (kg/m^2)	15.7-29.8	30.1-39.9	40.2-86.4
DVT, n (%)	54 (44.6)	52 (47.3)	20 (31.7)
PE, n (%)	67 (55.4)	58 (52.7)	43 (68.3)

Abbreviations: ABW, actual body weight; BMI, body mass index; DVT, deep-vein thrombosis; PE, pulmonary embolism.
[a]Data reported as mean ± SD.
[b]Significant difference, with P <0.05, between nonobese and severely obese groups and obese and severely obese groups.

Median time to therapeutic aPTT (hours:minutes) was 15:00 (IQR = 8:05-23:21) for the nonobese group, 15:40 (IQR = 9:22-25:10) for the obese group, and 15:22 (IQR = 7:54-23:40) for the severely obese group (P = 0.506). Subgroup analysis was completed for 140 patients who had at least 3 consecutive therapeutic aPTT values (60 non- obese, 52 obese, and 28 severely

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obese). The mean ± SD infusion rate for nonobese patients was 17.2 ± 5 U/kg/h based on ABW and 18.4 ± 5.6 U/kg/h based on DBW. Obese patients required a mean ± SD of 15.9 ± 4.4 U/kg/h based on ABW and 20.2 ± 5.7 U/kg/h based on DBW. Severely obese patients required a mean ± SD of 13.9 ± 3.9 U/kg/h based on ABW and 20.8 ± 6 U/kg/h based on DBW. A total of 29 patients (55.8%) and 13 patients (46.4%) in the obese and severely obese groups, compared with 21 (35%) in the nonobese group, required an infusion rate above the initial dose of 18 U/kg/h to achieve consecutive therapeutic aPTT values ($P = 0.087$).

Table 4 displays efficacy and safety outcomes. Bleeding events occurred in 14%, 13.6%, and 7.9% of nonobese, obese, and severely obese groups, respectively ($P = 0.453$). Catheter-directed tenecteplase was given in 17 patients (7 nonobese, 6 obese, and 4 severely obese), and systemic alteplase was administered in 6 patients (2 nonobese, 1 obese, and 3 severely obese). Of the patients who received a thrombolytic prior to heparin, 3 nonobese, 3 obese, and 0 severely obese experienced a bleeding event (33.3%, 42.9%, and 0%, respectively). There were no thrombotic events documented in any group.

Table 4. Outcomes.

	Nonobese (n = 121)	Obese (n = 110)	Severely Obese (n = 63)	P Value
Efficacy				
Time to therapeutic aPTT[a] [hours:minutes]	15:00 [8:05-23:21]	15:40 [9:22-25:10]	15:22 [7:54-23:40]	0.506
aPTT values[b]				
Percentage subtherapeutic	35.6 ± 26.7	37 ± 26.9	42.3 ± 25.4	NC
Percentage therapeutic	47.9 ± 24.2	51.8 ± 23.7	48.6 ± 23.4	NC
Percentage supratherapeutic	16.1 ± 19.3	11.2 ± 17.2	9.2 ± 14.8	NC
Safety				
Bleeding event, n (%)	17 (14)	15 (13.6)	5 (7.9)	0.453
Hgb drop ≥2 g/dL and ≥2 units PRBCs received[c]	4 (23.5)	3 (20)	0	NC
Discharge summary documentation[c]	17 (100)	13 (86.7)	5 (100)	NC
Thrombotic events, n (%)	0	0	0	NC
Thrombolytic received + Bleeding event, n (%)[d]	3/9 (33.3)	3/7 (42.9)	0/7	0.154

Abbreviations: aPTT, activated partial thromboplastin time; Hgb, hemoglobin; NC, not calculated; PRBCs, packed red blood cells.
[a]Data reported as median [IQR].
[b]Data reported as mean ± SD; percentage representative of all aPTT values while on heparin therapy.
[c]Percentages calculated out of patients with bleeding event.
[d]Percentages calculated as number of bleeding events in those receiving thrombolytic/total number receiving thrombolytic.

Discussion

Optimal heparin dosing has been controversial since the early 1990s and with increasing weight trends across the United States, the controversy continues. When heparin is used for the treatment of VTE, weight-based heparin dosing is recommended because it improves attainment of target aPTT values.[9] However, in patients categorized as obese or severely obese, there is currently no consensus on the most appropriate weight that should be used for dosing.[17] The nomogram proposed by Raschke et al[9] utilizes ABW. However, the study included patients with a mean weight of 80.9 kg, with only 9 of 62 (14.5%) patients weighing more than 100 kg.[9]

Studies by Hull et al[14] and Hirsh et al[15] suggest that VTE recurrence is reduced when the lower threshold of therapeutic is exceeded within 24 hours. In obese patients with a BMI >30 kg/m^2 treated with heparin for VTE, 89.3% of patients received a bolus dose less than the recommended 80 U/kg and 76.2% had an initial infusion rate below the recommended dose of 18 U/kg/h. This study describes a prescribing pattern of physicians approximating final therapeutic infusion rate based on experience instead of adhering to institutional protocol. They separately interviewed 8 physicians who stated that they were aware of weight-based dosing, but the large doses required for obese patients was concerning for bleeding events, leading them to decrease the dose.[8] Additionally, 28.6% and 14.3% of the study patients failed to achieve therapeutic aPTTs within 24 and 48 hours, respectively.[8] These results highlight the need to reassess and clearly define dosing strategies in the increasingly prevalent obese population.

With more than one-third of the US population being obese or severely obese, reevaluating the appropriate dosing strategy is important.[18] Literature on heparin dosing in the obese population is sparse and is further limited by lack of a standardized definition of obesity and calculation for DBW. Recent guidance for management of heparin in VTE suggests that a DBW may be an appropriate approach for obese patients.[17] In our cohort, a pharmacist managed heparin dosing protocol using a DBW for patients weighing greater than 20% over their IBW resulted in a therapeutic aPTT within approximately 15 hours of infusion initiation for nonobese, obese, and severely obese patients. Our protocol requires aPTT values to be ordered every 6 hours until a patient achieves 2 consecutive therapeutic aPTT values. We recognized that laboratory blood draws are often collected after the ordered time; therefore, a therapeutic aPTT value at approximately 15 hours likely represents the second aPTT.

To our knowledge, only 1 other study evaluating the use of a DBW for therapeutic heparin infusions exists. Fan et al[19] evaluated time to therapeutic aPTT with ABW and DBW in preimplementation and postimplementation of an institutional protocol. Their protocol calculated a DBW using the same formula as in our study. However, a DBW was used for all patients >30% over IBW, whereas ours utilized DBW for patients 20% over their IBW. The mean weight of the obese group in the preimplementation phase was 104.7 ± 11.5 kg, and only 31 patients (40.8%) achieved a therapeutic aPTT within 24 hours. After implementation of the DBW protocol, 44 patients (57.1%) achieved a therapeutic aPTT within 24 hours, and the mean weight of the postimplementation obese group 138.7 ± 35.6 kg. The infusion rate in the obese group to achieve a therapeutic aPTT was found to be 18.2 U/kg/h utilizing DBW, which correlates well with the Raschke nomogram.[9,10] Similar to our study, there was no difference found in bleeding events when using a DBW in obese patients.[19]

Rapidly exceeding the lower limit of therapeutic aPTT value lowers the risk of recurrent VTE, thus, making initial dosing and subsequent titrations crucial.[8,13,20] Shin and Harthan[21] utilized a weight-based dosing heparin protocol specific to medicine, neurology, and cardiac patients to evaluate time to exceed the lower limit of therapeutic aPTT. Utilizing ABW, they demonstrated mean $\pm$ SD time (in hours) to therapeutic aPTT for patients <100 kg, 100 to < 125 kg, 125 to < 150 kg, and $\geq$150 kg of 12.9 ± 9.2, 15.5 ± 12.9, 18.1 ± 15.8, and 23.8 ± 27.9, respectively (P = 0.002), suggesting that body weight affects the time to therapeutic aPTT.[21] Because heparin does not readily distribute into the less vascular adipose tissue, the dose requirements of heparin in obese patients are not directly proportional to their ABW.

A subgroup analysis of patients from our cohort with a stable therapeutic infusion demonstrated that DBW correlated more closely with our protocol dose of 18 U/kg/h. Obese and severely obese patients required doses of 20.2 ± 5.7 and 20.8 ± 6 U/kg/h, respectively, based on DBW. The nonobese population also closely aligned with DBW; however, DBW does not differ significantly from ABW in nonobese patients.

Our study had a slightly higher rate of bleeding events compared with other published studies. This may have been a result of our definition of bleeding, which included a decrease in hemoglobin with subsequent transfusion of PRBCs and/or documentation of bleeding in the discharge summary. Some other studies only included a hemoglobin decrease with transfusion of PRBCs. Similar to other studies evaluating heparin in obese populations, no difference in bleeding events was observed between the nonobese, obese, or severely obese groups.[19,21] We evaluated additional thrombotic events until patient discharge and found no additional thrombotic events in any of the patients included, which may be limited by our definition. We further analyzed bleeding in patients who received thrombolytic agents prior to heparin initiation. No difference in bleeding was found between the nonobese, obese, or severely obese patients, with 33.3% (3/9), 42.9% (3/7), and 0% (0/7), respectively, in patients who received a thrombolytic.

Our study is limited by the single-center cohort and retrospective design. Much like the current literature, our study is also limited by the overall small sample size and the lower number of patients in the severely obese weight category. Use of the discharge summary to identify documentation of bleeding and/or thrombotic events may have underestimated adverse bleeding events and/or secondary thrombotic events. Additionally, our primary outcome of time to therapeutic aPTT does not necessarily correlate with achievement of steady state, especially because only 47.6% of our patient population had 3 consecutive therapeutic aPTTs, and we did not assess time to exceed the lower limit of therapeutic aPTT. We did not include baseline characteristics that might put patients at increased risk of VTE, such as active cancer or preexisting hypercoagulability states, or increased risk for bleeding, including concomitant use of anticoagulants and antiplatelet agents or preexisting renal dysfunction. We also did not investigate indications for administration of thrombolytic agents.

Conclusion
The median time to therapeutic aPTT did not differ in nonobese, obese, or severely obese patients when a DBW was utilized in patients weighing 20% over their IBW. Our findings support the use of a DBW for patients weighing 20% over their IBW.

Declaration of Conflicting Interests

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