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Venous Thromboembolism Prophylaxis in Low Body Weight Critically Ill Patients

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Abstract

Objective: To compare bleeding and thromboembolic events in low body weight patients receiving reduced-dose venous thromboembolism (VTE) prophylaxis versus standard-dose VTE prophylaxis.**Design:** Multicenter, retrospective, cohort study.**Setting:** Five Ascension Health Hospitals.**Patients:** Adult, critically ill, low body weight (≤50 kg) patients who received either reduced-dose VTE prophylaxis (n = 140) or standard-dose VTE prophylaxis (n = 279) for at least 48 h.**Intervention:** Reduced-dose prophylaxis (enoxaparin 30 mg daily or heparin 5000 units every 12 h subcutaneously) or standard-dose prophylaxis (enoxaparin 40 mg daily, enoxaparin 30 mg every 12 h, or heparin 5000 units every 8 h subcutaneously).**Measurements and Main Results:** A total of 419 patients were included with a mean weight of 45.1 ± 4.2 kg in the standard-dose group and 44.0 ± 5.1 kg in the reduced-dose prophylaxis group ($P = .02$). The primary endpoint, composite bleeding, was significantly lower in patients receiving reduced-dose prophylaxis (5% vs 12.5%, $P = .02$). After adjusting for confounding factors, results remained consistent demonstrating reduced composite bleeding with reduced-dose prophylaxis (odds ratio: 0.36, 95% confidence interval: 0.14-0.96). Major bleeding events occurred in 3.6% of reduced-dose patients compared with 8.6% in standard-dose patients ($P = .056$). Clinically relevant nonmajor bleeding (5.4% vs 2.9%, $P = .24$) and VTE (2.2% vs 0%, $P = .08$) events were similar between groups.**Conclusions:** A reduced-dose VTE prophylaxis strategy in low body weight, critically ill patients was associated with a lower risk of composite bleeding and similar rate of thromboembolism.

Keywords

enoxaparin, prophylaxis, low body weight, unfractionated heparin, venous thromboembolism

Introduction

Nearly 900 000 individuals are diagnosed with venous thromboembolism (VTE) in the United States each year, resulting in 300 000 deaths annually associated with pulmonary embolism.[1,2] Venous thromboembolism poses a major threat for hospitalized patients, as it is estimated that two-thirds of events occur during or following a hospital admission.[1] Critically ill patients are at a higher risk of developing VTE as they often have multiple risk factors including increased age, immobility, surgical procedures, malignancy, mechanical ventilation, and central venous catheters.[3] To reduce the risk of VTE, unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) are recommended for prophylaxis.[4]

Although the use of chemoprophylaxis is an effective strategy to decrease the risk of VTE, healthcare providers must consider the risk of bleeding.[5–7] Risk factors associated with an increased risk of bleeding are common in critically ill patients including thrombocytopenia, renal replacement therapy, concomitant antiplatelet therapy, severe liver disease, and surgical procedures.[5] When evaluating therapeutic anticoagulation, previous literature has demonstrated an increased risk of bleeding in low body weight patients. However, limited data exist to evaluate the risk of bleeding in low body weight patients receiving VTE prophylaxis.[8,9] Rojas et al studied the association between anti-Xa activity during enoxaparin prophylaxis in patients with a weight of 55 kg or less. This study demonstrated an inverse correlation exists, as patients in the lowest body weight group experienced the highest anti-Xa factor levels.[10] Notably, this study did not assess the clinical impact of high anti-Xa levels.

Current guidelines suggest LMWH or UFH to reduce the incidence of VTE; however, frequency and dose of prophylaxis remain controversial for low body weight patients.[4,11] A single-center study evaluating underweight, critically ill patients reported

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a higher rate of clinically relevant bleeding with standard-dose versus reduced-dose prophylaxis. Notably, this study included a limited number of patients receiving reduced-dose prophylaxis, as it was only prescribed to 15.3% of the study population.[12] A more recent study evaluating VTE prophylaxis in underweight patients concluded that patients receiving standard dosing were nearly 5 times more likely to experience a major bleed than those in the reduced-dose group. Limitations of this study include a lack of critically ill patients and a major bleeding definition which included a hemoglobin drop ≥ 2 g/dL in the absence of bleeding.[13]

Insufficient evidence exists to guide the appropriate dosing of VTE prophylaxis in critically ill patients with low body weight. The goal of this study is to compare the safety and efficacy of standard versus reduced-dose VTE prophylaxis in critically ill patients with low body weight.

Methods

We conducted a multicenter, retrospective cohort study to evaluate reduced versus standard-dose VTE prophylaxis and the association with bleeding and VTE in adult, low body weight, critically ill adult patients. This study was conducted at 5 hospitals within Ascension Health from January 2015 to September 2022. An electronic medical record shared between the individual hospital sites was used to review patient records. Subjects were included if they were admitted to an intensive care unit, had an admission weight $\leq$50 kg, and received VTE chemoprophylaxis with UFH or enoxaparin for greater than 48 h. Patients were excluded if they were admitted with a suspected VTE or acute bleeding event, received thrombolytics/therapeutic anticoagulation during admission, or were diagnosed with a coagulopathy prior to admission. Coagulopathy was defined as either an inherited bleeding (eg, hemophilia, von Willebrand disease) or clotting (eg, factor V leiden, factor II mutation) disorder.[14,15] Reduced-dose VTE prophylaxis was defined as heparin 5000 units subcutaneously every 12 h or enoxaparin 30 mg subcutaneously daily. Standard-dose VTE prophylaxis was defined as heparin 5000 units subcutaneously every 8 h, enoxaparin 40 mg subcutaneously daily, or 30 mg subcutaneously every 12 h. Patients were included into a respective study group if they had received 50% or greater of the total available doses during their admission. Venous thromboembolism prophylaxis (drug/dose) was ordered at the discretion of the treating clinician. An institutional VTE prophylaxis guideline provided recommendations for dose adjustment in patients less than 50 kg, however, required the pharmacist to contact the prescriber to discuss modification of the order. Only the first patient encounter during the study period was included; institutional review board approval was obtained prior to study initiation.

The primary outcome is the incidence of composite bleeding (in-hospital major bleeding + clinically relevant nonmajor bleeding [CRNMB]) between patients who received standard versus reduced-dose prophylaxis. In accordance with International Society on Thrombosis and Haemostasis criteria, major bleeding was defined as bleeding that is fatal, or symptomatic bleeding that is defined as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, intramuscular with compartment syndrome, or bleeding that results in a decrease in hemoglobin 2 g/dL or more and requires 2 units of blood or more.[12] Clinically relevant nonmajor bleeding was defined as any sign or symptom of hemorrhage that does not fit the criteria of major bleeding but requires medical intervention, leading to hospitalization or requires an in-person evaluation.[16,17] Secondary outcomes included the comparison of individual components of the composite bleeding endpoint and thromboembolic events during the hospital admission (VTE or pulmonary embolism).

Baseline demographics, including the Charlson Comorbidity Score and IMPROVE Risk Score for Venous Thromboembolism, were collected.[18–20] Venous thromboembolism prophylaxis regimens were evaluated for the duration of the hospital admission. If a dose adjustment was made during the hospital admission, the number of doses received prior to and following the dose adjustment was collected. Medications with the potential to impact the risk of bleeding (eg, aspirin, P2Y12 inhibitors, antidepressants, and nonsteroidal inflammatory agents) were assessed during the hospital admission. Creatinine clearance was calculated according to the Cockcroft-Gault formula. Acute kidney injury (AKI) was assessed using the KDIGO AKI criteria.[21] Mild hepatic disease was defined as chronic hepatitis B or C infection or cirrhosis without portal hypertension. Moderate hepatic disease was defined as cirrhosis with portal hypertension without variceal bleeding. Severe hepatic disease was defined as cirrhosis with portal hypertension and history of variceal bleeding.[17] For patients with a surgical procedure, the risk of bleeding was assessed using the procedural bleed risk appendix from the American College of Cardiology's Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation.[22] Manual chart review was performed in order to collect data points and assess for an association with anticoagulation.

Sample Size

Buckheit et al found that 7.3% of underweight, critically ill patients who received standard-dose VTE prophylaxis experienced a major bleed, while 1.6% of those who received reduced dose experienced a major bleed.[13] To find a significant difference based on these values, with an alpha error rate of 0.05% and 80% power, a sample size of 205 study participants in each group was necessary, for a total of 410 study participants. However, due to a lower frequency of patients receiving reduced-dose prophylaxis in our study, we amended our study to collect patients in a 2:1 ratio, which resulted in 279 patients in the standard-dose group, 140 patients in the reduced-dose group, for a total of 419 study participants.

Statistical Analysis

Descriptive statistics were calculated to characterize the study participants. Continuous variables were described as the mean

with standard deviation; categorical variables were described as frequency distributions. Univariable analysis was completed using Student *t* test for the comparison of continuous data and the Mann-Whitney *U* test for the comparison of non-normal continuous data between various groups. Univariable analysis for categorical data was completed using the χ^2 test. Multivariable analysis was performed utilizing logistic regression. Two models were utilized, the first with all potential confounding variables included if associated (theoretically and statistically) with the outcome *or* different between groups with a *P* value less than .1. The second model used a backward elimination model with a removal *P* value of .2 with a goal of decreasing the total number of variables in the model. All data was analyzed using SPSS v. 28.0 and a *P* value less than .05 indicates statistical significance.

Results

A total of 419 patients met inclusion criteria, with 279 patients in the standard-dose group and 140 patients in the reduced-dose group (Figure 1). Baseline characteristics are described in Table 1. The average weight in patients receiving standard-dose prophylaxis was 45.1 ± 4.2 kg versus 44 ± 5.1 kg in patients receiving reduced dose ($P = .02$). Anticoagulant characteristics are described in Table 2. In the standard-dose group, more patients received heparin (67%); in the reduced-dose group, more patients received enoxaparin (70%). Anticoagulant dose switching occurred more frequently in patients receiving reduced versus standard-dose prophylaxis (34.3% vs 16.1%, $P < .01$). Medications that increase the risk of bleeding were assessed between the 2 groups. Patients in the standard-dose group more frequently received aspirin (35.1% vs 22.9%, $P = .01$) and NSAIDs (12.2% vs 2.9%, $P < .01$). There were no significant differences in patients receiving P2Y12 inhibitors (9.3% vs 9.0%, $P = .91$) or antidepressants (6.5% vs 2.6%, $P = .06$). Dual antiplatelet use was similar between groups (6.8% vs 7.1%, $P = .9$) while single antiplatelet use was more frequent in the standard-dose group (30.5% vs 17.9%, $P < .01$).

The primary outcome, composite in-hospital bleeding, was significantly lower in patients who received reduced-dose VTE prophylaxis (5% vs 12.5%, $P = .02$). After adjusting for confounding factors as shown in Table 3, similar results were observed favoring the reduced-dose prophylaxis group (odds ratio [OR]: 0.36, 95% confidence interval [CI]: 0.14-0.96). In a subgroup analysis evaluating each agent, there was no significant difference between agents for composite bleeding event; enoxaparin 40 mg daily (11.1%), enoxaparin 30 mg twice daily (0%), heparin 5000 units every 8 h (13.4%), enoxaparin 30 mg daily (6.1%), and heparin 5000 units every 12 h (2.4%), ($P = .13$). Substituting length of stay for duration of VTE prophylaxis led to almost identical results in the regression (OR: 0.41, 95% CI: 0.17-0.99). Furthermore, removing COVID patients also led to a similar estimate in the regression (OR: 0.40, 95% CI: 0.16-0.1.00).

Results for secondary outcomes such as major bleeding events, CRNMB events, and VTE events are described in Table 4. Major bleeding events occurred in 3.6% of reduced-dose patients compared with 8.6% in standard-dose patients ($P = .056$). No difference was observed in CRNMB (5.4% vs 2.9%, $P = .24$) and VTE (2.2% vs 0%, $P = .08$) between the standard and reduced groups, respectively.

Discussion

Venous thromboembolism prophylaxis is commonly used in critically ill patients to prevent thrombosis during hospital admission; however, safety data are limited in patients with low body weight. Overall, we observed that the use of reduced-dose prophylaxis was associated with a 60% decrease in the odds of composite bleeding after adjusting for confounders. These results may have been driven by major bleeding, suggesting a possible benefit to utilizing a reduced-dose regimen. There was no significant difference between the groups' rates of VTE, suggesting that a reduced-dose strategy in critically ill patients with low body weight may be considered.

Our findings have similarities and differences to previously published research. A single-center, retrospective cohort study

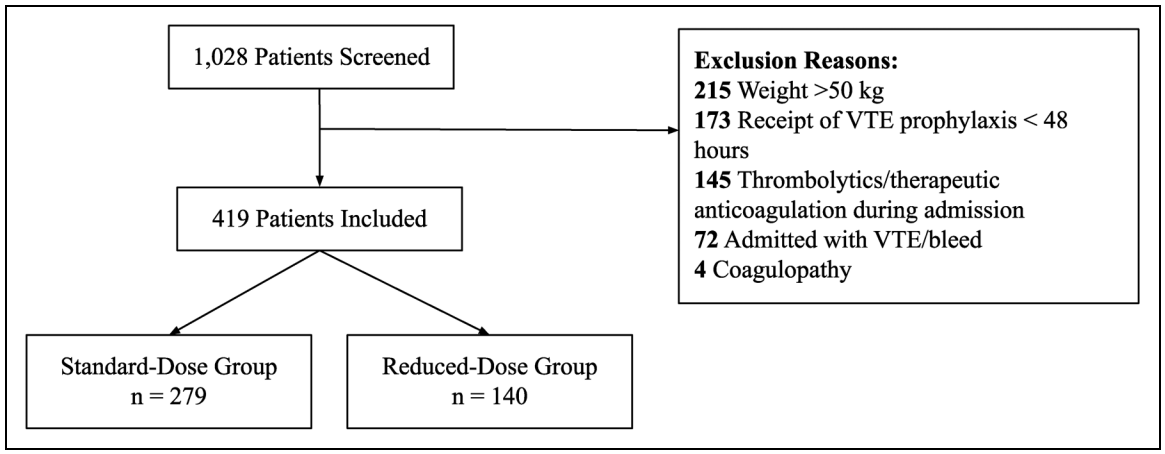

Figure 1. Patient selection.

	Standard group (n = 279)	Reduced group (n = 140)	*P* value
Age (years)	66.2 ± 16.9	68.8 ± 18.4	.15
Female	198 (71.0%)	111 (79.3%)	.07
Weight (kg)	45.1 ± 4.2	44.0 ± 5.1	.02
Creatinine clearance (mL/min)	39.2 ± 21.8	35.9 ± 19.0	.13
Baseline hemoglobin	11.5 ± 2.4	11.7 ± 2.4	.22
Baseline platelet	259.2 ± 124.5	280.2 ± 139.4	.07
Comorbidities			
Myocardial infarction	27 (9.7%)	14 (10%)	.92
Chronic kidney disease	34 (12.2%)	7 (5%)	.02
Atrial fibrillation	19 (6.8%)	7 (5%)	.47
Stroke	34 (12.2%)	16 (11.4%)	.82
Dementia	32 (11.5%)	20 (14.3%)	.41
COPD	72 (25.8%)	33 (23.6%)	.62
Rheumatologic disease	6 (2.2%)	3 (2.1%)	.99
Peripheral vascular disease	13 (4.7%)	7 (5%)	.88
Peptic ulcer disease	4 (1.4%)	1 (0.7%)	.52
Diabetes	52 (18.6%)	20 (14.2%)	.38
Hemiplegia	3 (1.1%)	2 (1.4%)	.61
AIDS/HIV	4 (1.4%)	2 (1.4%)	.99
VTE	14 (5%)	2 (1.4%)	.07
Hepatic disease			
Mild disease	7 (2.5%)	1 (0.7%)	.52
Moderate/severe disease	4 (1.4%)	1 (0.7%)	
Malignancy			
Active cancer	39 (14.0%)	29 (20.7%)	.07
History of any malignancy	60 (21.5%)	36 (25.7%)	.33
Metastatic solid tumor	15 (5.4%)	14 (10.0%)	.11
COVID-19	4 (1.4%)	7 (5%)	.03
Acute kidney injury (AKI)			
No AKI	151 (54.1%)	70 (50.0%)	0.98
Stage 1	68 (24.4%)	38 (27.1%)	
Stage 2	42 (15.0%)	22 (15.7%)	
Stage 3	18 (6.5%)	10 (7.2%)	
SOFA Score	4.9 ± 3.3	4.9 ± 3.2	.76
IMPROVE VTE Score	2.5 ± 1.2	2.5 ± 1.2	.27
Charlson comorbidity	2.1 ± 2.3	2.2 ± 2.6	.10
Procedural bleed risk			
None	222 (79.6%)	118 (92.1%)	.30
Low	4 (1.4%)	0 (0%)	
Intermediate	14 (5.0%)	8 (2.9%)	
High	39 (14.0%)	14 (5.0%)	
Hospital length of stay	8.7 (5.5-15.8)	7.9 (4.8-11.3)	.01
ICU length of stay	3 (2-6)	3 (1-5)	.68
VTE prophylaxis duration	7 (4-13)	6 (4-10)	.01

Table 2. Anticoagulation Characteristics.[a]

	Standard group (n = 279)	Reduced group (n = 140)
Enoxaparin 40 mg SQ every 24 h	90 (32.3%)	0 (0%)
Enoxaparin 30 mg SQ every 12 h	2 (0.7%)	0 (0%)
Heparin 5000 units every 8 h	187 (67%)	0 (0%)
Enoxaparin 30 mg every 24 h	0 (0%)	98 (70%)
Heparin 5000 units every 12 h	0 (0%)	42 (30%)
Regimen switch during admission	45 (16.1%)	48 (34.3%)

[a]Data expressed as n (%).

by Carter et al assessed bleeding and incidence of VTE in underweight, critically ill patients receiving standard-dose (15,000-22,500 U/day of UFH and enoxaparin 40 mg/day or 30 mg twice daily) or reduced-dose prophylaxis (<15,000 U/day of UFH or <40 mg/day of enoxaparin).[12] This study found a difference in all bleeding and no difference in CRNMB, which is similar to our study.[12] However, this study had a smaller sample size than our study (n = 295), as only 15.3% (n = 45) of patients received reduced-dose prophylaxis.

Studies evaluating VTE prophylaxis in noncritically ill patients have shown mixed results. Buckheit et al noted that underweight

Table 3. Composite Bleeding—Adjusted Analysis.

Variables	Odds ratio	95% confidence interval	*P* value
Model 1: All variables with differences between groups or associated with outcome at $P < .1$			
Reduced versus standard	**0.36**	**0.14-0.96**	**.04**
Age	1.02	0.99-1.05	.11
Baseline hemoglobin	0.87	0.74-1.02	.09
Baseline platelets	1.00	0.99-1.00	.31
Weight	0.98	0.90-1.07	.60
History of stroke	2.54	1.05-6.12	.04
Major bleed within 90 days of admission	10.25	1.08-96.92	.04
VTE prophylaxis duration	1.06	1.01-1.11	.01
History of COPD	0.42	0.16-1.12	.08
DAPT	2.19	1.28-3.75	<.01
SAPT	0.74	0.30-1.85	.52
Medium or high surgical bleed risk	1.79	0.78-1.79	.17
Female	0.68	0.30-1.57	.68
CKD	0.91	0.27-5.14	.78
VTE history	0.76	0.11-2.09	.20
Active cancer	1.30	0.83-2.04	.26
COVID	1.34	0.14-13.05	.80
SSRI/SNRI/TCA	1.97	0.56-6.99	.29
NSAID	1.44	0.50-4.17	.50
Model 2: Reduced model with backward elimination			
Reduced versus standard	**0.38**	**0.15-0.94**	**.04**
Age	1.02	0.99-1.04	.16
Baseline hemoglobin	0.87	0.75-1.02	.08
History of stroke	2.30	0.99-5.36	.05
Major bleed within 90 days of admission	10.60	1.50-74.9	.02
VTE prophylaxis duration	1.07	1.02-1.11	<.01
History of COPD	0.46	0.18-1.21	.08
DAPT	2.14	1.32-3.48	<.01

Table 4. Secondary Outcomes.

Outcome	Standard group (n = 279)	Reduced group (n = 140)	*P* value
Major bleeding	24 (8.6%)	5 (3.6%)	.056
CRNMB requiring medical intervention	15 (5.4%)	4 (2.9%)	.24
Venous thromboembolism	6 (2.2%)	0	.08

Abbreviation: CRNMB, clinically relevant nonmajor bleeding.

patients receiving standard-dose prophylaxis were nearly 5 times more likely to experience a major bleed compared to reduced-dose prophylaxis (OR: 4.73, 95% CI: 1.05-21.34) with similar rates of CRNMB and VTE.[11] Of note, this study defined major bleeding as an isolated hemoglobin decrease without receipt of blood transfusion, which was listed as the most frequent reason for major bleeding. Furthermore, a study by Nemeth et al which evaluated underweight patients receiving either standard-dose or reduced-dose enoxaparin found no difference between the 2 dosing groups for composite bleeding (6.5% vs 7.8%, $P = .496$) and VTE events (0% vs 0.8%, $P = .674$).[23] However, the study excluded surgical/trauma patients and patients with severe hepatic disease and/or renal failure.

Notably, while the dose of therapeutic anticoagulation is weight-based; prophylactic doses of these same drugs are fixed regimens. This may predispose low body weight patients to adverse effects related to increased drug exposure. This theory is supported by a study evaluating enoxaparin for VTE prophylaxis in low body weight patients, which demonstrated an inverse correlation between weight and anti-Xa activity. Furthermore, peak anti-Xa levels $\geq$0.5 IU/mL were present in 60% of patients.[10] We further add to this literature as we observed an increased risk of bleeding in critically ill low body weight patients receiving standard-dose VTE prophylaxis during this study period.

Strengths of this study include that we were able to achieve sufficient statistical power through the use of our multicenter design, which enabled us to include a significantly larger number of patients in the reduced-dose prophylaxis group, in contrast to prior studies mentioned. However, this study was limited by its retrospective design, which could be affected by unmeasured confounders. The study groups were also unevenly distributed between each agent, as the majority of the standard group received heparin while the reduced-dosed group received enoxaparin. Finally, some patients switched between standard-dose and reduced-dose prophylaxis. However, this would have decreased the ability to observe a difference between groups, which was not the case for our primary outcome.

Conclusion

A reduced-dose VTE prophylaxis strategy in critically ill patients with low body weight was associated with a lower risk of composite bleeding and similar rate of thromboembolism. Based on these results, it may be beneficial to consider using a reduced-dose VTE prophylaxis in these patients.

Declaration of Conflicting Interests

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