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Unfractionated heparin versus enoxaparin for venous thromboembolism prophylaxis in intensive care units: a propensity score adjusted analysis

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Abstract
Venous thromboembolism (VTE) is a common complication in hospitalized patients. Pharmacologic prophylaxis is used in order to reduce the risk of VTE events. The main purpose of this study is to compare the prevalence of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients admitted to the intensive care unit (ICU) who received unfractionated heparin (UFH) versus enoxaparin as VTE prophylaxis. Mortality was evaluated as a secondary outcome. This was a Propensity Score Adjusted Analysis. Patients admitted to neurology, surgical, or medical ICUs and screened with venous doppler ultrasonography or computed tomography angiography for detection of VTE were included in the analysis. We identified 2228 patients in the cohort, 1836 (82.4%) patients received UFH and 392 (17.6%) patients received enoxaparin. Propensity score matching yielded a well-balanced cohort of 950 (74% UFH, 26% enoxaparin) patients. After matching, there was no difference in prevalence of DVT (RR 1.05; 95% CI 0.67–1.64, p = 0.85) and PE (RR 0.76; 95% CI, 0.44–1.30, p = 0.31). No significant differences in location and severity of DVT and PE between the two groups were detected. Hospital and intensive care unit stay was similar between the two groups. Unfractionated heparin was associated with a higher rate of mortality, (HR 2.04; 95% CI, 1.13–3.70; p = 0.019). The use of UFH as VTE prophylaxis in ICU patients was associated with a similar prevalence of DVT and PE compared with enoxaparin, and the site and degree of occlusion were similar. However, a higher mortality rate was seen in the UFH group.

Keywords Venous thromboembolism · Deep vein thrombosis · Pulmonary embolism · Heparin · Enoxaparin

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Highlights

- Venous thromboembolism remains highly prevalent in hospitalized patients, and often leads to increased mortality and cost burden during hospitalization and post-discharge.
- Intensive care unit patients have a greater risk of thrombotic events due to additional risk factors such as immobilization, mechanical ventilation, and central catheters.
- The result of this study supports the use of either drug in prevention of VTE. The rates, location and degree of occlusion for both DVT and PE were similar between the two groups.
- In this propensity score matching analysis, a higher number of mortality was observed in the UFH group.
- Further studies are warranted to assess the safety of using enoxaparin as a first line.

Introduction

The use of chemical prophylaxis with unfractionated heparin (UFH) as well as low-molecular-weight heparin (LMWH) has been shown to reduce the prevalence of venous thromboembolism (VTE) events in hospitalized patients [1, 2, 3, 4]. One of the earliest studies to compare the efficacy of UFH with enoxaparin, as thromboprophylaxis in patients with major trauma was a randomized, double-blind trial by Geerts and colleagues [5]. They found that enoxaparin was more effective than UFH in preventing deep vein thrombosis (DVT) and major bleeding was comparable between the two groups [5]. In a recent large systematic review of venous thromboprophylaxis in critically ill patients (medical and stroke), the results revealed that LMWH had a small impact on mortality. LMWH showed reductions in pulmonary embolism (PE), symptomatic deep vein thrombosis (DVT), but estimates were imprecise, with very small benefits [6]. Therefore, the American Society of Hematology 2018 guideline panel felt that the certainty of these estimated effects was related as very low due to high risk of bias and imprecision of the estimates. Overall, the panel recommend either LMWH or UFH for critically ill patients [7].

Although both agents are used widely in intensive care units, the preference to use one over the other depends mainly in renal function or risk of bleeding complications [8, 9]. Enoxaparin has the disadvantage that it accumulates in patients with renal failure and therefore has the potential to produce serious bleeding in such patients [10]. Additionally, its longer half-life and lack of complete reversal of anticoagulation poses a greater risk for major bleeding. Therefore, UFH is preferred in patients with substantial bleeding risk.

Venous thrombosis is categorized based on the severity of occlusion (partial or total occlusion) and site of occlusion (superficial vs deep vein, lower extremity vs upper extremity). Unlike deep veins, superficial veins have no surrounding muscles to squeeze and dislodge a blood clot. For these reasons, superficial venous thrombosis rarely causes a blood clot to break loose (embolism) and poses less risk for PE [11]. However, a superficial vein thrombosis is still treated with anticoagulation depending on the location and extent of the thrombus. Lower extremity DVT can further be classified into proximal and distal (also known as calf DVT). In inpatient studies, 80% of all diagnosed DVTs are proximal, and 20% are calf [12]. However, some outpatient DVT studies report a proportion of calf DVT as high as 60% to 70%, underlining the potential relevance of the problem in everyday clinical practice [12]. The location of the DVT has a substantial impact on its ability to break off and travel to the pulmonary vasculature, causing a PE. Proximal DVT is more likely to cause a PE than a distal DVT and is managed with therapeutic anticoagulation [13, 14, 15, 16, 17].

The objective of our study is to compare the prevalence of venous thromboembolism, both DVT and PE, in critically ill patients from intensive care units receiving either LMWH, as enoxaparin or UFH subcutaneously. Our population included patients from three different settings of intensive care units (medical, surgical, and neurology). A secondary aim was to classify the DVT and PE based on location; upper extremity (subclavian, axillary, brachial) or lower extremity (greater saphenous, superficial femoral, deep femoral, popliteal, below the calf), (unilateral or bilateral) and degree of occlusion (partial versus total occlusion) or (main or saddle, lobar, interlobar, segmental, subsegmental) and presence of right heart strain to determine whether unfractionated heparin versus enoxaparin, as VTE prophylaxis, is associated with a greater severity of deep vein thrombosis or pulmonary embolism.

We hypothesized that unfractionated heparin for thromboprophylaxis is associated with an increased risk of developing deep vein thrombosis, pulmonary embolism or death among patients hospitalized in the intensive care unit.

Methods

This is a single center, retrospective cohort study. Propensity score matching was performed to reduce the effects of confounding by ensuring baseline characteristics were similar between the two treatment groups. The study protocol was reviewed and approved by the Committee for the Protection of Human Subjects (CPHS, the governing Institutional Review Board) and Memorial Hermann Hospital, with a waiver of informed consent.

We analyzed the Vizient database ((Vizient, Inc.Ft. Worth, TX). from January 2015 until June 2019. In this database, 22,744 patients were admitted to three intensive care units (ICU): neuro ICU, (NICU), surgical ICU (SICU), and medical ICU (MICU). Of those, 11,688 were admitted to NICU; 5251 were in SICU, and 5805 were in MICU. The inclusion criteria were patients aged 18 years and older who were admitted to any of the three ICUs, received VTE prophylaxis with either UFH or enoxaparin, and underwent venous doppler ultrasonography (VDU) of the all extremities including bilateral upper and lower, or lower or upper extremities for assessment of DVT. We also included patients who underwent chest computed tomography angiography (CTA) during their hospitalization period. We then excluded 20,102 admissions because no VDU was completed, resulting in inclusion of 2228 patients [1404 in NICU, 313 in SICU, and 511 in MICU]. (Fig. 1). In Table 1, baseline characteristics included disease severity, defined as the extent of organ system derangement or decompensation and risk of mortality provides a medical classification to estimate the likelihood of in-hospital death for a patient,

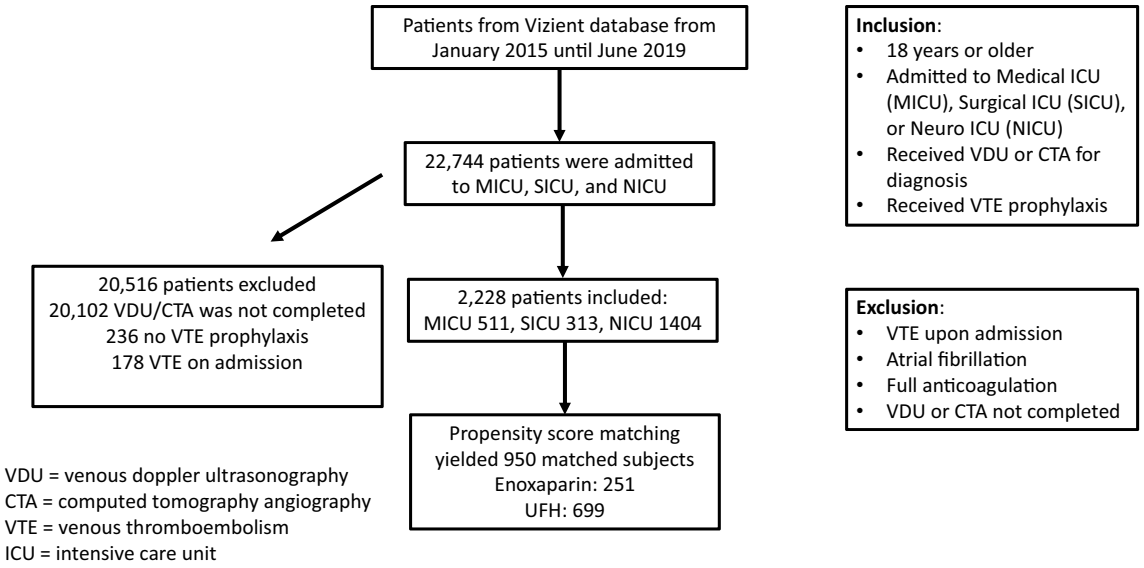

Fig. 1 Flow chart

as scores ranging from 1 to 4 as either minor, moderate, major, or extreme. All patient refined—Diagnosis Related Grouping (APR-DRG), Severity of Illness (SOI), and Risk of Mortality (ROM) are proprietary outputs of the APR-DRG Grouper, owned by 3MTM [18]. VTE was defined as DVT confirmed by ultrasonography or PE diagnosed on CTA regardless of symptoms or physical exam findings. All perioperative PE or proximal DVT as a secondary diagnosis were included. PE diagnosed on chest computed tomography angiography (CTA) was collected on those who underwent screening with or without VDU. Exclusion criteria consisted of any patient who had VTE upon admission, atrial fibrillation, or required full anticoagulation therapy outside of a new VTE event during admission. Pharmacological VTE prophylaxis was administered within 48 hours of admission or surgery in the absence of contraindications [19, 20]. Early mobilization was also initiated as soon as possible. The primary outcome was prevalence of VTE. Secondary outcomes included overall survival, time to DVT/PE diagnosis, site of occlusion, burden of clot, and ICU and hospital length of stay.

Statistical analysis

Propensity score matching

We preformed propensity score matching to control for potential confounding factors. Prior to matching, we identified 2228 patients in the cohort, 1836 (82.4%) patients received UFH and 392 (17.6%) patients received enoxaparin. The distributions of the patient characteristics were compared using Mann–Whitney U or Fisher's exact test. Propensity scores were computed by fitting a logistic regression model on the patients who had complete data. The covariates used for balancing are the following: age, gender, admission diagnosis (surgical, medical, trauma), mechanical ventilation, renal function, risk of mortality, doppler use, PE-CTA, and central vein catheter. After computing propensity scores, nearest neighbor matching with a 1:4 ratio and a caliper of 0.5 was done. A well-balanced cohort of 950 matched subjects with 251 in the enoxaparin group and 699 in the UFH group was included in the analysis for comparing outcomes. After matching, standardized mean differences for the covariates were close to 0, indicating adequate balance (Fig. 2). After checking for quality of cohort balance, treatment effects on the two matched cohorts of 950 patients were tested. A binary generalized liner model with a binomial family and a log link was applied to the data. In the models of PE, we also included placement of filter (vena cava filter placement) as a covariate. For continuous outcomes, ordinary linear regression model was used, and log transformation was applied when the outcomes were skewed.

Kaplan–Meier survival curve and cox proportional hazard model

We conducted additional statistical analyses to assess the impact of enoxaparin or UFH thromboprophylaxis upon the mortality and VTE outcome variables. Overall survival time was defined as the time interval from admission date to the mortality date and was censored at the last day of hospital stay. Time to DVT/PE was defined

Table 1 Patient Characteristics Before Matching

Category	Enoxaparin (n = 392)	Heparin (n = 1836)	p-value
Age	50 (30–64)	60 (46–70)	< 0.001
Ethnicity (Hispanic)	76 (19)	306 (17)	0.209
Race	–	–	0.004
African American	59 (15)	360 (20)	–
Caucasian/White	147 (38)	508 (28)	–
All Other	181 (46)	939 (51)	–
Gender, Male	267 (68)	1061 (58)	< 0.001
Weight-Kg	81 (68–98)	81 (68–99)	0.869
Mechanical Ventilation	66 (17)	713 (39)	< 0.001
Renal Function	302 (93)	1008 (74)	< 0.001
Severity of Illness	–	–	0.090
Minor	7 (2)	15 (1)	–
Moderate	21 (5)	70 (4)	–
Severe	78 (20)	336 (18)	–
Extreme	285 (73)	1415 (77)	–
Risk of Mortality	–	–	0.002
Minor	21 (5)	56 (3)	–
Moderate	44 (11)	126 (7)	–
Severe	105 (27)	361 (20)	–
Extreme	221 (57)	1293 (70)	–
PICC	7 (2)	32 (2)	1.000
CVC	11 (3)	129 (7)	0.001
Patient per service line	–	–	0.002
Neurology	166 (42)	1238 (67)	–
Surgical	137 (35)	176 (10)	–
Medical	89 (23)	422 (23)	–
Doppler indication	–	–	0.002
No Surveillance/Diagnostic	98 (25)	171 (9)	–
Surveillance	165 (42)	837 (46)	–
Diagnostic	129 (33)	828 (45)	–
Vena cava filter placement	13 (3)	74 (4)	0.568
First doppler from admission, days	4 (2–8)	4 (2–7)	0.855
Doppler versus no doppler	–	–	< 0.001
No doppler	120 (31)	229 (13)	–
Doppler	272 (69)	1607 (88)	–
Doppler type	–	–	0.002
All extremity doppler	61 (22)	643 (40)	–
Lower extremity doppler	110 (40)	396 (25)	–
Upper extremity doppler	52 (19)	167 (10)	–
Multiple oppler orders	49 (18)	401 (25)	–
PE-CTA	184 (47)	562 (31)	< 0.001
Patient Type	–	–	0.002
All Surgery	176 (48)	857 (50)	–
Medical	82 (22)	807 (47)	–
Trauma	110 (30)	68 (4)	–
VTE risk category	–	–	0.068
High risk	344 (94)	1657 (96)	–
Low risk	18 (5)	47 (3)	–
Moderate risk	4 (1)	27 (2)	–
Very low risk	2 (0.5)	3 (0.2)	–

Data are median (Inter quartile range) or no. (%) of patients. All surgery (craniectomy, craniotomy, general), *CTA* computed tomography angiography, *CVC* central venous catheter *PICC* peripherally inserted central catheter, *PE* pulmonary embolism, *VTE* venous thromboembolism, Renal function = Creatinine Clearance > 30 ml/min

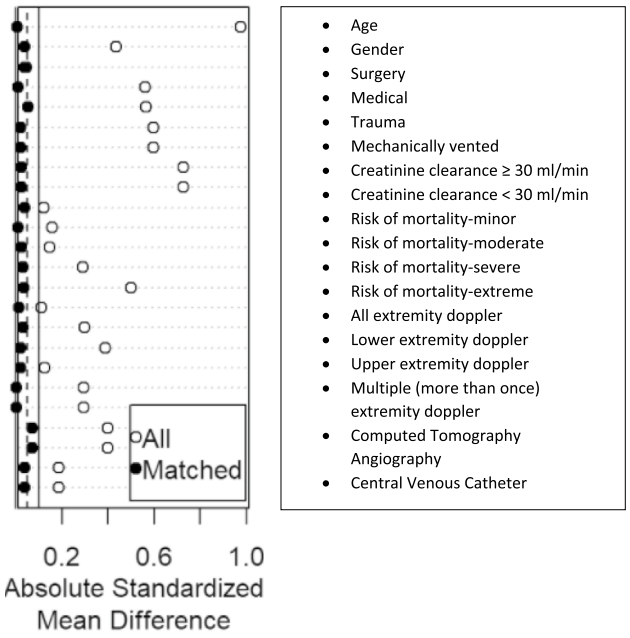

Fig. 2 Propensity analysis: Examining the balance of the matching. The covariates used for balancing are the following: age, gender, admission diagnosis (surgical, medical, trauma), mechanical ventilation, renal function, risk of mortality, doppler use, PE-CTA completed (yes or no), and central vein catheter. After computing propensity scores, nearest neighbor matching with a 1:4 ratio and a caliper of 0.5 was done. A well-balanced cohort of 950 matched subjects (251 in the enoxaparin group and 699 in the unfractionated heparin group) were included in the subsequent analysis for comparing the outcomes. As seen in the plot, the balance of the covariates was improved by the matching. An absolute standardized mean difference close to zero means good balance

as the time interval from admission date to the time of DVT/PE and was censored by the last day of hospital stay time while death was treated as a competing outcome. Cox proportional hazard model and cause-specific Cox model were used, and Kaplan–Meier survival curves were plotted. (Fig. 3).

Results

We identified 2228 patients in the cohort, 1836 (82.4%) patients received UFH and 392 (17.6%) patients received enoxaparin**.** (Table 1). Over 90% of the UFH group were on UFH 5000 IU three times a day and the enoxaparin group was mainly receiving 30 mg every 12 hours with only a few receiving 40 mg daily. Very few doses fell outside of these dosages. Propensity score matching yielded a well-balanced cohort of 950 patients (UFH, 74% and enoxaparin 26%). (Table 2) After matching, there was no difference in prevalence of DVT during ICU stay between UFH and enoxaparin treatment groups, respectively (propensity score adjusted Relative Risk (RR) of UFH vs. enoxaparin 1.05; 95% Confidence Interval (CI), 0.67–1.64, p = 0.85), nor was there a difference in time to diagnosis of DVT (Hazard Ratio (HR) 1.19; 95% CI, 0.74–1.91, p = 0.475). (Table 3) Furthermore, there was no statistically significant difference among the two treatment groups in terms of presence of upper extremity DVT (RR 0.79; 95% CI, 0.28–2.25, p = 0.66) or lower extremity DVT (RR 1.17; 95% CI, 0.62–2.19, p = 0.63). Additionally, degree of occlusion (partial versus total),

Fig. 3 Kaplan Meier survival curves of all cause mortality

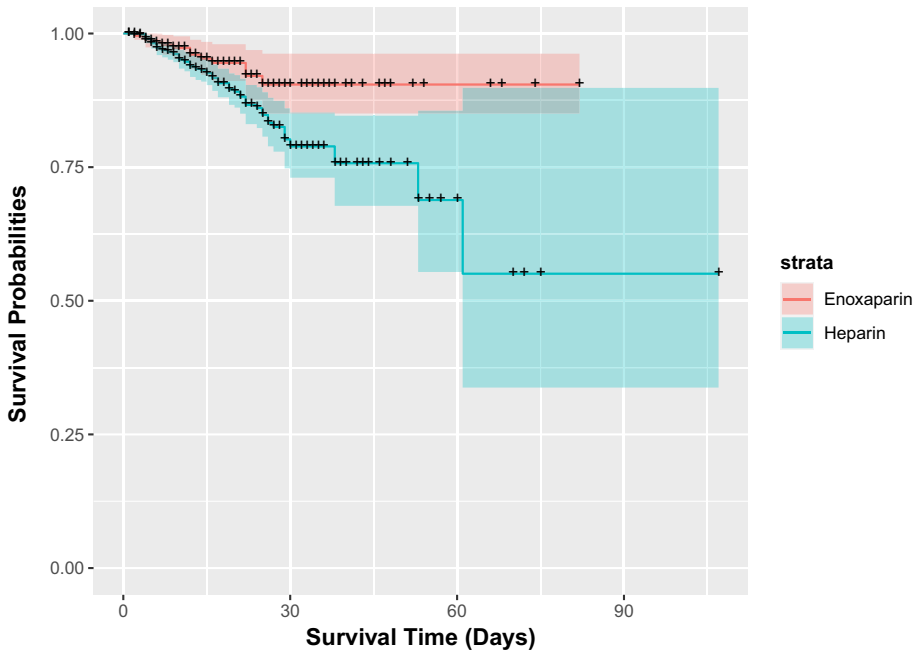

Table 2 Patient characteristics after matching

Category	Heparin (n = 699)	Enoxaparin (n = 251)	p-value
Age	57 (42–67)	52 (36–67)	0.029
Gender, Male	437 (63)	163 (65)	0.542
Patient type	–	–	0.050
All Surgery	396 (57)	141 (56)	–
Medical	243 (35)	75 (30)	–
Trauma	60 (9)	35 (14)	–
Mechanical ventilation	208 (30)	60 (24)	0.086
Renal function	625 (89)	228 (91)	0.627
Risk of mortality	–	–	0.230
Minor	33 (5)	17 (7)	–
Moderate	71 (10)	29 (12)	–
Severe	155 (22)	64 (26)	–
Extreme	440 (63)	141 (56)	–
Doppler type	–	–	0.070
All extremity doppler	179 (26)	47 (19)	–
Lower extremity doppler	178 (26)	70 (28)	–
Multiple doppler orders	120 (17)	36 (14)	–
Upper extremity doppler	70 (10)	33 (13)	–
No doppler	152 (22)	65 (26)	–
PE-CTA	278 (40)	108 (43)	0.370
CVC	24 (3)	6 (2)	0.530

Data are median (Inter quartile range) or no. (%) of patients. All surgery (craniectomy, craniotomy, general), *CTA* computed tomography angiography, *CVC* central venous catheter, *PICC* peripherally inserted central catheter, *PE* pulmonary embolism, *VTE* venous thromboembolism, Renal function = Creatinine Clearance > 30 ml/min

location of the clot or whether the DVT was present bilaterally in both upper and lower extremities were similar. (Table 3).

There was no difference in prevalence of PE during ICU stay between UFH and enoxaparin treatment groups, respectively (propensity score adjusted RR 0.76; 95% CI, 0.44–1.30, p = 0.31). No significant differences in location and severity of pulmonary embolism between the two groups were detected (propensity score adjusted RR 0.84; 95% CI, 0.22–3.22, p = 0.80 [saddle or main], RR 2.51; 95% CI, 0.31–20.37, p = 0.39 [interlobar], RR 1.08; 95% CI, 0.40–2.94, 0.88 [lobar], RR 0.83; 95% CI, 0.4–1.71, p = 0.61 [segmental], RR 0.68; 95% CI, 0.31–1.50, p = 0.34 [subsegmental]), right heart strain (propensity score adjusted RR 0.63; 95% CI, 0.19–2.13, p = 0.46). (Table 3).

Figure 3 shows Kaplan–Meier curves for the overall survival probabilities of the matched unfractionated heparin and enoxaparin cohorts. UFH was associated with higher rate of mortality, (HR 2.04; 95% CI, 1.13–3.70, p = 0.019). Hospital and intensive care unit stay was similar between the two groups.

Discussion

The primary outcome was to compare the prevalence of DVT and PE between the two groups, and we did not see any difference. Nor was there a difference in the location, severity, time of diagnosis, or initiation of DVT prophylaxis. However, our secondary outcome of interest was mortality difference between the two drugs. The unfractionated heparin was associated with a higher rate of mortality compared to enoxaparin after controlling for potential confounders using propensity-matched analysis.

This study has several important limitations. This is a retrospective observational study, and as such it is prone to bias. We performed propensity score matching in order to mitigate for the role of potential confounding factors. The two cohorts were balanced using necessary covariates required to minimize variation. The observation of increased mortality reported with UFH could be unrelated to VTE and due to unknown confounders for which we were not able to control. While our study is a well-matched cohort, this mainly relates to the variables that were included in the propensity score. The other potential limitation of the study was the requirement for patients to have undergone VDU. Table 1 shows a higher number of VDU completed in the UFH group. However, overall utilization of VDU in

Table 3 Clinical outcomes of VTE and mortality after matching

Outcome	Enoxaparin (n = 251)	Heparin (n = 699)	RR	95% CI	p-value
PE	17 (7)	35 (5)	0.76	0.44–1.30	0.314
Saddle artery	3 (1)	7 (1)	0.84	0.22–3.22	0.797
Interlobar	1 (0.4)	7 (1)	2.51	0.31–20.4	0.388
Lobar	5 (2)	15 (2)	1.08	0.40–2.94	0.884
Segmental	10 (4)	23 (3)	0.83	0.40–1.71	0.607
Sub-segmental	9 (4)	17 (2)	0.68	0.31–1.50	0.339
Bilaterally PE	3 (1)	11 (2)	1.32	0.37–4.69	0.671
Right Heart Strain	4 (2)	7 (1)	0.63	0.19–2.13	0.456
DVT	23 (9)	67 (10)	1.05	0.67–1.64	0.845
Upper extremity DVT	5 (2)	11 (2)	0.79	0.28–2.25	0.659
Internal jugular	3 (1)	11 (2)	1.32	0.37–4.69	0.671
Subclavian	3 (1)	6 (1)	0.72	0.18–2.86	0.64
Axillary	3 (1)	9 (1)	1.08	0.29–3.95	0.911
Brachial	7 (3)	12 (2)	0.62	0.24–1.55	0.302
Upper DVT—total occlusion	2 (1)	13 (2)	2.33	0.53–10.3	0.263
Upper DVT—partial occlusion	11 (4)	17 (2)	0.55	0.26–1.17	0.122
Lower extremity DVT	12 (5)	39 (6)	1.17	0.62–2.19	0.632
Common femoral	7 (3)	27 (4)	1.39	0.61–3.14	0.436
Greater saphenous	3 (1)	4 (1)	0.48	0.11–2.13	0.333
Superficial femoral	10 (4)	19 (3)	0.68	0.32–1.45	0.32
Deep femoral	5 (2)	10 (1)	0.72	0.25–2.08	0.542
Popliteal	3 (1)	16 (2)	1.92	0.56–6.53	0.299
Lower DVT—total occlusion	4 (2)	11 (2)	0.99	0.32–3.08	0.983
Lower DVT—partial occlusion	12 (5)	37 (5)	1.11	0.59–2.09	0.754
Bilaterally DVT	4 (2)	10 (1)	0.90	0.28–2.84	0.854
Mortality	13 (5)	67 (10)	1.85	1.04–3.29	0.036
Hospital LOS	14 (8–23)	14 (8–21)	–	–	0.159
ICU LOS	6 (3–13)	8 (4–13)	–	–	0.090

Data are median (Inter quartile range) or no. (%) of patients. *CI* confidence interval, *DVT* deep vein thrombosis, *ICU* intensive care unit, *LOS* length of stay, *PE* pulmonary embolism, *RR* relative risk

ICUs was low. Recently, consensus guidelines have deemphasized the use of asymptomatic clots detected via screening as a clinically-relevant outcome [21, 22, 23, 24, 25, 26]. However, we feel that these asymptomatic cases cannot be dismissed and that each case should be evaluated individually. Lastly, we did not evaluate for bleeding complications in both agents. However, prior studies found both agents to be safe. [15, 27, 28]

In previous studies, the overall difference between the two drugs in preventing DVT and PE were deemed comparable and acceptable alternatives to use either drug. In looking at individual studies, Laporte and colleagues preformed individual patient data meta-analysis of enoxaparin vs unfractionated heparin for venous thromboembolism prevention in medical patients. In this meta-analysis, the enoxaparin cohort significantly reduced rates of VTE and all-cause mortality compared to the unfractionated heparin cohort [27]. A large study involving over 3000 patients, also favored enoxaparin in reducing VTE in hospitalized patients when compared to unfractionated heparin [29]. However, guidelines have concluded to use either anticoagulant as VTE prophylaxis after analyzing the evidence presented by all studies that otherwise suggested the use of enoxaparin might be preferable in reducing VTE and all cause-mortality. It is indeed important to use guidelines that have systematically evaluated studies to reach a recommendation. In doing so, one should keep in mind that statistical heterogeneity could potentially either overestimate or underestimate the true effect of the intervention. It might be difficult to reach a conclusion based on risk of bias and effect sizes. However, our study and previously mentioned publications emphasize the need to investigate further the potential benefit of enoxaparin in intensive care unit patients.

Conclusion

Overall, the result of the study shows the rates, location and degree of occlusion for both DVT and PE were similar between the two groups. However, in-hospital mortality is associated with use of subcutaneous unfractionated heparin in intensive care units. Unfortunately, no additional laboratory values to suggest cause of death were collected, as this was not the primary outcome of interest. In future analysis, it may be prudent to collect cause of death and laboratory values pertaining to outcomes of interest, such as venous thromboembolism and mortality.

Author contributions There is no financial support to disclose. SS developed the initial concept and design. SS, WL, AC, and LM contributed to the study's conduct and interpretation of results. SS and KD drafted the manuscript. WL, KD, JC, TN, DM, AK, TD, JB, AC and LM provided critical revisions of the manuscript for important intellectual content.

Data availability All data analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

Declarations

Conflict of interest Sophie Samuel, Wen Li, Koren Dunn, Jennifer Cortes, Thuy Nguyen, Daniel Moussa, Abhay Kumar, Thanh Dao, James Beeson, H Alex Choi, Louise D McCullough declare that they have no conflict of interest.

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