Safety and Efficacy of Enoxaparin Compared With Unfractionated Heparin for Venous Thromboembolism Prophylaxis in Hemodialysis Patients

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Abstract

Background: Enoxaparin, a low-molecular-weight heparin approved for prophylaxis in patients at risk for venous thromboembolism (VTE), offers several advantages compared with unfractionated heparin (UFH). Enoxaparin is primarily excreted through renal elimination and is currently not recommended in patients receiving hemodialysis (HD) due to potential increased bleeding complications. To date, there are limited safety and efficacy data supporting the use of enoxaparin in this patient population for VTE prophylaxis. **Objective:** The aim of this study was to compare the safety and efficacy of enoxaparin with UFH for deep venous thromboembolism (DVT) prophylaxis in medically ill HD patients. **Methods and Results:** This retrospective cohort study examined medically ill patients who received HD and were concomitantly prescribed enoxaparin or UFH for at least 2 consecutive days for VTE prophylaxis. A total of 225 patients (150 received UFH and 75 received enoxaparin) were evaluated in chronological order. The primary outcome was a composite of major, clinically relevant nonmajor, and minor bleeding based on International Society on Thrombosis and Haemostasis bleeding definitions. The secondary outcome was the occurrence of a confirmed thrombotic event. Baseline characteristics were similar between the cohorts. One patient in each cohort had a documented bleed (UFH = 0.7%, enoxaparin = 1.3%, $P > .05$) during the admission assessed; however, neither bleed was related to the prophylactic agent utilized. No patients developed a VTE during the index hospitalization. **Conclusions:** This study demonstrates that enoxaparin may be as safe and effective as UFH for VTE prophylaxis in medically ill patients receiving HD.

Keywords

heparin, enoxaparin, venous thromboembolism, prophylaxis, dialysis

Introduction

Enoxaparin is a low-molecular-weight heparin (LMWH) approved by the US Food and Drug Administration in 1993 for prophylaxis in patients at risk for deep venous thrombosis (DVT) and pulmonary embolism (PE).¹ Compared with unfractionated heparin (UFH), enoxaparin offers several advantages when used for thromboprophylaxis, including improved bioavailability, a longer half-life leading to less frequent dosing, a more predictable dose-response, and less thrombocytopenia.^{2–4} Eliminated primarily through the kidneys, enoxaparin exerts its anticoagulant effect by inactivating factor Xa.⁵ While a 30% dose reduction is recommended for patients with renal dysfunction, enoxaparin is not removed during dialysis and could therefore cause increased bleeding complications.^{1,2,4,6}

To date, the safety and efficacy of enoxaparin for venous thromboembolism (VTE) prophylaxis has not been well established for patients receiving hemodialysis (HD) due to a lack of supporting data. In a retrospective study evaluating

enoxaparin for DVT treatment in morbidly obese patients, renal dysfunction (defined as serum creatinine [SCr] >1.4 mg/dL) was not associated with increased bleeding. A multivariate analysis was performed analyzing independent risk factors associated with bleeding. Female gender, warfarin use, enoxaparin dose <0.9 mg/kg, and duration of enoxaparin use >48 hours were independent risk factors for bleeding.⁷ Despite the fact that this study looked at DVT treatment dosing, renal dysfunction was not associated with increased bleeding. Therefore, prophylactic enoxaparin dosing may not be associated with increased bleeding risk in patients with renal dysfunction.

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Enoxaparin may potentially be safe and effective in HD patients; however, more trials are needed to confirm this. The purpose of this study was to compare the safety and efficacy of enoxaparin with UFH for VTE prophylaxis in medically ill HD patients.

Methods

Study Design and Patients

This single-center, retrospective, cohort study evaluated patients at a 450-bed community hospital. Prior to data collection, this study was approved by the institutional review board. Informed consent was not necessary due to the retrospective nature of the study.

Any patient who received HD with at least 2 consecutive days of concomitant VTE prophylaxis with enoxaparin 30 mg daily or UFH 5000 units every 8 hours was screened for enrollment. International Classification of Diseases 9 and 10 codes were utilized to identify patients who received HD during their hospital admission. Patients admitted September 1, 2014, through December 31, 2016, were evaluated in chronological order, or until 150 patients were included in each cohort. The start date of September 1, 2014, was selected because the hospital changed dialysis filters in August 2014. Patients were excluded if they received therapeutic anticoagulation. Patients were also excluded if they received UFH 7500 units every 8 hours, UFH 5000 units twice daily, >1 standard dose of enoxaparin for VTE prophylaxis (≥ 40 mg), or if they changed prophylaxis agents during their hospitalization. These regimens were excluded to appropriately evaluate the efficacy of VTE prophylaxis dosing recommendations in patients with renal dysfunction; by controlling these variables, the internal validity of the study and reproducibility of the results were augmented. If patients did not receive HD, received continuous renal replacement therapy, received peritoneal dialysis (PD), resided in the intensive care unit at any point during the hospitalization, or underwent surgery during the hospitalization, they were also excluded.

Outcomes

The primary outcome was a composite of bleeding events attributed to enoxaparin or UFH during the index hospitalization. Bleeding events were assessed and categorized as major, clinically relevant nonmajor, or minor using International Society on Thrombosis and Haemostasis (ISTH) bleeding definitions. Major bleeding was defined per ISTH as fatal bleeding, and/or symptomatic bleeding in a critical area or organ (such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome), or confirmed bleeding causing a decrease in hemoglobin (Hgb) level of 2 g/dL or more, and transfusion of 2 or more units of packed red blood cells (PRBCs). Clinically relevant nonmajor bleeding was defined as overt bleeding not meeting criteria for

Figure 1. Patient Inclusion and Exclusion.

Note. CRRT= continuous renal replacement therapy; DC= discontinued; HD = hemodialysis; ICU = intensive care unit; MAR = medication administration record; PD = peritoneal dialysis; UFH = unfractionated heparin.

major bleeding but requiring medical intervention (skin hematoma of ≥ 25 cm², epistaxis or gingival bleeding ≥ 5 minutes, or rectal bleeding). All bleeds that were not considered major or nonmajor bleeding events were categorized as minor bleeds.^{8,9} Given the retrospective nature of this study, a source of bleeding had to be documented in the patient's electronic medical record to confirm an event, as to prevent falsely elevated bleeding rates. Similarly, a drop in Hgb of 2 g/dL or more was not considered a bleed if there was no acute blood loss or bleeding event documented. In addition, if a patient received PRBCs upon admission and was not on prophylaxis, this was not considered a bleed from one of the prophylaxis regimens. These criteria were selected to prevent overestimation of bleeding events in a patient population with a high usage of erythropoietin-stimulating agents due to anemia of chronic kidney disease (CKD).

Secondary outcomes evaluated the occurrence of confirmed DVT or PE during the hospital admission assessed. A confirmed DVT or PE was defined based on imaging results for each patient during that admission. Imaging results included Doppler ultrasounds of the lower extremities, chest computed tomography (CT), and D-dimer. The PADUA score was selected to assess each patient's risk for thrombosis.¹⁰

Statistical Analysis

Baseline demographics, as well as primary and secondary outcomes, were analyzed using the Student *t* test for continuous

Table 1. Baseline Characteristics.

Characteristic, n (%) ^a	UFH (n = 150)	Enoxaparin (n = 75)	P value
Age, y, mean ± SD	67.8 ± 14.7	67.2 ± 13.8	.749
Male	90 (60)	46 (61.3)	.847
Race			.034
Caucasian	102 (68)	47 (62.7)	
Black	37 (24.7)	22 (29.3)	
Asian	1 (0.7)	5 (6.7)	
Other	3 (2)	0 (0)	
Unknown	7 (4.7)	1 (1.3)	
BMI, mean ± SD ^b	29.8 ± 6.9	30.5 ± 9.1	.569
LOS, mean ± SD	7.9 ± 5.5	4.9 ± 2.8	<.05
Heparin boluses with HD	130 (86.7)	65 (86.7)	1.000
AST ^c	143.9 ± 1235.7	63.3 ± 242.9	.592
ALT ^c	115.5 ± 948.2	55.7 ± 265.7	.608
SCr	5.97 ± 3.3	6.28 ± 3.6	.528
Aspirin	97 (64.7)	43 (57.3)	.285
PADUA score components			
Active cancer	0 (0)	0 (0)	NA
History of VTE	8 (5.3)	3 (4)	.756
Reduced mobility	144 (96)	59 (78.7)	<.05
Thrombophilia	0 (0)	0 (0)	NA
Active infection	99 (66)	46 (61.3)	.491
Recent trauma or surgery	5 (3.3)	1 (1.3)	.666
Heart failure	20 (13.3)	8 (10.7)	.568
Respiratory failure	36 (24)	17 (22.7)	.824
Acute MI	4 (2.7)	0 (0)	.304
Acute stroke	3 (2)	1 (1.3)	1
Rheumatic disease	0 (0)	0 (0)	NA
Hormonal therapy	0 (0)	0 (0)	NA
PADUA score, mean ± SD	4.2 ± 1.3	3.5 ± 1.4	<.05
Concomitant antithrombotics			
Prasugrel	2 (1.3)	0 (0)	.554
Ticagrelor	0	0	NA
Clopidogrel	36 (24)	16 (21.3)	.655
Alteplase	3 (2)	0 (0)	.553
Dipyridamole	1 (0.7)	1 (1.3)	1

Note. ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; HD = hemodialysis; LOS = length of stay; MI = myocardial infarction; NA = not applicable; SCr = serum creatinine; UFH = unfractionated heparin; VTE = venous thromboembolism.

^an (%) unless otherwise specified.

^bNote that 6 patients in the UFH arm and 4 patients in the enoxaparin arm were missing either height or weight and BMI could not be calculated on these patients.

^cNote that 6 patients in the UFH arm and 6 patients in the enoxaparin arm were missing AST/ALT from the labs upon admission.

data and chi-square or Fisher exact test for categorical data. A *P* value of <.05 indicated statistical significance. Analyses were performed with IBM SPSS Statistics for Windows.

Results

A total of 812 patients were screened for inclusion. Once a total of 150 patients were evaluated chronologically in the heparin cohort, the remaining heparin patients were excluded (*n* = 160). Patients in the enoxaparin cohort were evaluated chronologically, yielding 75 patients. The most common reasons for exclusion between both groups were changing

prophylaxis regimens during the hospitalization assessed (54 patients), or if they had surgery during the hospitalization assessed (52 patients). In addition, patients in the UFH group were often excluded if they received <2 days of prophylaxis (88 patients). See Figure 1 for a complete list of exclusions.

Baseline characteristics were similar between groups. The mean age for each cohort was 67 years. The majority of patients in each group were Caucasian males (Table 1). Patients in the UFH cohort had a mean length of stay (LOS) of 7.9 days, while the mean LOS was 4.9 days (*P* < .05) in the enoxaparin cohort. This translated to a mean of 18 doses of UFH and 4.4 doses of enoxaparin administered during the

Table 2. Outcomes.

Outcome, n (%)	UFH (n = 150)	Enoxaparin (n = 75)	P value
Leg Doppler ultrasounds confirming VTE	0 (0)	0 (0)	NA
Chest CT confirming VTE	0 (0)	0 (0)	NA
VQ scan confirming VTE	0 (0)	0 (0)	NA
Elevated D-dimer	0 (0)	0 (0)	NA
Documented bleed	1 (0.7)	1 (1.3)	1
Documented bleed related to prophylaxis	0 (0)	0 (0)	NA
Major bleed	0 (0)	0 (0)	NA
CRNM	0 (0)	0 (0)	NA
Minor bleed	0 (0)	0 (0)	NA

Note. CRNM = clinically relevant non-major; CT = computed tomography; NA = not applicable; UFH = unfractionated heparin; VTE = venous thromboembolism.

study period. Heparin boluses associated with HD treatment were provided to 86.7% of patients in each cohort. Other concomitant antithrombotics utilized in the study population included prasugrel, clopidogrel, and alteplase. The alteplase doses included were those administered to maintain central venous catheter clearance; all other doses of alteplase were excluded. Neither group had a statistically significant difference in use of these medications.

A PADUA score of ≥ 4 points indicates a need for VTE prophylaxis.¹⁰ Based on the mean PADUA score, enoxaparin patients did not require prophylaxis for the hospital admissions assessed. The UFH cohort had a mean PADUA score of 4.2 and the enoxaparin cohort had a mean PADUA score of 3.5 ($P < .05$). There were statistically more patients in the UFH cohort who had reduced mobility when compared with the enoxaparin cohort, 144 patients (96%) and 59 (78.7%), respectively ($P < .05$). The other components of the PADUA score were not statistically different.

One patient in each study cohort had a documented bleed during the admissions assessed. However, neither bleed was related to the prophylaxis agent utilized. The patient in the UFH cohort experienced acute blood loss anemia secondary to a gastrointestinal bleed. The patient in the enoxaparin cohort presented with vaginal bleeding and acute blood loss anemia. Both patients were provided 2 units of PRBCs; however, neither bleeding event was attributed to the prophylactic agent received during their hospitalization because the patients were stabilized before a prophylaxis agent was initiated. An Hgb drop ≥ 2 g/dL occurred in 15 patients (10%) in the UFH cohort and in 5 patients (6.7%) in the enoxaparin cohort ($P = .408$). In the UFH group, 4 patients (2.7%) required ≥ 2 units of PRBCs while on VTE prophylaxis, whereas 1 patient (1.3%) in the enoxaparin group required ≥ 2 units of PRBCs ($P = .667$). All patients received PRBCs due to anemia of CKD. No patients developed a VTE during the study period.

Discussion

This study illustrates that enoxaparin 30 mg daily may be as safe and effective as UFH 5000 units every 8 hours for VTE prophylaxis in medically ill patients receiving HD. Although only 1 patient in each cohort had a bleeding event, no patients in either cohort experienced a bleeding event directly attributed to the prophylactic regimen administered during their hospitalization.

There are several limitations within this study. Patients were only included from a single-center, community hospital, and the sample size was limited. The small sample size might not have been adequately powered to detect a difference in bleeding events between cohorts. In addition, the retrospective nature of this study limited data extraction only to information that was documented in the patient's electronic health record. Physicians were also able to make decisions about the patient's care during the study period, so outcomes from this study could be affected by their decisions. If any decisions were undocumented, this could lead to misrepresentation of the study's results. Another limitation includes the differing hospitalization durations between treatment groups. Enoxaparin is renally eliminated and could accumulate over an extended period of time in patients receiving HD. As the enoxaparin cohort had a shorter LOS, there is a chance that the incidence of bleeding is underrepresented. In addition, the patients in the enoxaparin cohort had a lower thromboembolic risk. Based on the average PADUA score of 3.5, patients who received enoxaparin may not be at risk for developing a VTE.¹⁰

Previous studies have demonstrated similar results. A retrospective comparative effectiveness analysis by Chan and colleagues analyzed chronic HD and PD patients initiated on subcutaneous enoxaparin or UFH for the prevention of DVT and PE.¹¹ The primary end point was bleeding that resulted in hospitalization or death within 120 days of enoxaparin or heparin treatment initiation. Low doses (up to 60 mg of enoxaparin) were injected daily. Enoxaparin and UFH were equivalent in terms of bleeding risk (risk ratio [RR] = 0.98; 95% confidence interval [CI] = 0.78-1.23; P for equivalence = .02), and enoxaparin was noninferior in terms of thrombosis (RR = 0.77; 95% CI = 0.49-1.22; $P = .04$ for noninferiority).¹¹ Higher than standard doses recommended for patients with renal impairment were utilized in dialysis patients without increased bleeding risks.

The results of the present study, as well as the study by Chan and colleagues, suggest enoxaparin and UFH may be similar in terms of bleeding and thrombotic risk. Chan and colleagues utilized a dose of enoxaparin that was greater than the standard recommended dose for prophylaxis in patients with renal dysfunction. Yet, even when patients were provided a higher dose, there was an equivalent bleeding risk between the enoxaparin and UFH treatment groups. The current study utilized standard doses of enoxaparin based on package insert recommendations for patients with a

creatinine clearance <30 mL/min. The results suggest that the bleeding and thrombotic risk between enoxaparin 30 mg daily and UFH 5000 units every 8 hours cohorts may be similar. Future randomized, controlled trials are needed to confirm these findings.

Author Contributions

MSG, KBT, and ARB participated in the research and article preparation. All authors have approved the final article.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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