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Enoxaparin Administration Times and Hospital Length of Stay in Venous Thromboembolism Treatment: A Retrospective Study

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ABSTRACT

Background and objectives: Variations in enoxaparin administration times after orders in Computerized Physician Order Entry (CPOE) can increase the risk for bleeding and Venous thromboembolism (VTE) episodes and consequently increase hospital length of (LOS). Because of limited studies, the objective of the proposed retrospective cohort study was to evaluate the association of variations enoxaparin administration times and the hospital LOS.

Methods: Data were extracted from the study hospital's pharmacy order system and electronic medical records. Adult inpatient aged 18-87 years at a Northeast US hospital (from June 2013-June 2015) who had received at least two treatment doses of enoxaparin for VTE were identified. Patient characteristics, enoxaparin administration time differences (between order and first dose (<=2, >2 h), and between first and second dose (<18, 18-24, and >=25 h)) and hospital LOS days were collected.

Results: Of 275 patients, 134, 79 and 62 had DVT, PE, and both, respectively. The majority of the 275 patients received first enoxaparin dose after 2 h from order (>2 h, 58%, 160/275 vs. <=2 h, 41%, 115/275). About 33%, 61%, 5% patients received the second dose within 18 h, 18 to 24 h, and beyond 25 or more hours, respectively, after having received the first dose of enoxaparin. However, hospital LOS did not differ between the patient groups by first or second enoxaparin dose administration timings.

Conclusion: Although the variations in enoxaparin administration timing were significant, hospital LOS did not significantly correlate with enoxaparin administration time differences. However, there was a not significant trend toward patients receiving delayed first dose beyond 2 h and earlier second doses within 18 h of the first dose which had a times of the first dose from order entry and second dose from the first dose could increase the risk of DVT, PE or both that warrant further attention of hospital providers, policy makers, and future researchers. With the new CPOE system implementation shortly, steps need to be taken to improve documentation adverse events and optimize administration timing of medications in hospitals.

INTRODUCTION

Economic burden

Venous thromboembolism (VTE) is the third most common cardiovascular disease followed by myocardial infarction and stroke, causing significant morbidity and mortality worldwide [1]. About 900,000 people are affected with VTE each year in the United States (U.S.) and about 300,000 of them die from this disease [2]. In the U.S. alone, about 375,000 to 425,000 newly diagnosed, medically treated incident VTEs conservatively cost the US healthcare system from $7 billion to $10 billion per year [1,3]. Additionally, for the first hospitalization of VTE, it is estimated that the cost ranges from $3,000 to $9,500 per patient [1]. Further, average incremental direct medical costs were $12,000 to $15,000 (2014 US dollars) per treatment of an acute VTE among first-year survivors, controlling for risk factors [3]. Additionally, conservative cumulative cost estimates were $18,000-23,000 when there are subsequent complications for every incident VTE [3]. A recent study suggests any intervention that changes the length of stay in the hospital could significantly reduce hospitalization costs [1].

Venous thromboembolism treatment

Anticoagulants are used to treat VTE including both deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT is the formation of a blood clot in a deep vein usually in the lower leg, thigh or pelvis. The most serious complication of a VTE is the dislodging of clots, traveling to the lungs and resulting in a PE [4]. Once diagnosed, therapeutic levels of anticoagulation should be achieved as quickly as possible. Treatment goals for DVT include stopping clot propagation and prevention of recurrence of thrombosis, and the occurrence of PE and pulmonary hypertension [5]. The American College of Chest Physicians Guidelines recommends either Low Molecular Weight Heparin (LMWH), unfractionated heparin (UFH) or fondaparinux for an acute event of DVT or PE [6]. Enoxaparin (Lovenox) was the first LMW heparin approved by the U.S. FDA for treatment of DVT and PE in a dosage of 1 mg /kg twice daily or 1.5 mg/kg once daily [7].

Medication administration discrepancies in computerized provider order entry (CPOE) systems

Medication administration discrepancies persist despite the implementation of electronic ordering systems. Although CPOE systems reduce prescribing errors by conveying legible orders electronically to nurses and pharmacists, they do not prevent administration errors or timing discrepancies. In CPOE systems, orders are placed by a physician, verified by the pharmacy and then administered by the nursing staff. Unfortunately, up to 38% of inpatient medication errors occur at the administration stage [8]. Individual CPOE systems, such as Sunrise, automatically schedule daily dosing regimens to be administered at 9 am daily, due to ease of administration for nursing staff. Delays in administration of critical medications for conditions, such as PE, could potentially be life-threatening [2-9].The National Patient Safety Agency suggests that hospitals should define targeted timeframes for administering first doses and loading doses of key medications, such as anticoagulants [8-10].For example, for enoxaparin to work properly with the desired effect, not only does the first dose need to be given immediately for the patient to be fully anticoagulated, but also subsequent doses are to be given according to the Q24 h schedule. The administration times for the first two doses were selected as variables because, after the second dose, the CPOE system fixes the dose timing to every 24 h. To our knowledge, there are no set guidelines on how quickly anticoagulation needs to be started for inpatient VTE treatments.

Study rationale and objectives

Discrepancies in enoxaparin administration times from order to 1st dose and subsequent 2nd dose may occur in CPOE systems. Differences in timing treatments could contribute to increasing the hospitalization costs of VTE. However, from a preliminary literature review, there were no retrospective studies on the association of varying enoxaparin administration times and Hospital Length of Stay (LOS). Thus, little is known about the time of enoxaparin administered after its CPOE in the hospital system and its association with hospital outcome of hospital LOS in the real-world setting. Because of the lack of such published data in the literature, from a hospital perspective, the authors proposed a retrospective study to evaluate the current CPOE system with regards to enoxaparin dosing time and hospital LOS. The current study is of great interest as it applies to implementing processes related to the quality of care of patients receiving enoxaparin in study hospital using a COE system. Second, this will inform the study hospital's pharmacy department and others about potential improvements required to hospital pharmacy policies for medication use systems in the future when electronic medical records are in place for optimal treatment efficacy, safety, and hospital outcomes.

The study objectives were to determine the timing of enoxaparin administration when using COE with an automated scheduling system and the association of timing of administration with hospital length of stay outcomes. The hypothesis is that variations (either too early or delayed) in the timing of enoxaparin dosing may be associated with increased LOS. The specific objectives of the study in VTE treatment were:

1. When the first dose of enoxaparin was administered.

2. To determine the time difference between when the first dose of enoxaparin and the second dose of enoxaparin were given.

3. To compare the LOS days between patients who received the dose of enoxaparin within the desired time and patients who received either too early.

METHODS

Study design

This study was designed as an observational retrospective cohort study.

Setting

The study hospital is an 819-bed acute care teaching hospital located in Hartford, Connecticut. About 42,000 inpatient visits were made every year as well as 100,000 outpatient visits and about 100,000 emergency department visits.

Data sources

Data were collected from the study hospital's CPOE system, WORx Pharmacy Order System, and Sunrise Clinical Manager (All scripts Healthcare, Chicago, IL) using chart review of electronic medical records. The study hospital's institutional review board approved the use of the deffidentified data for the retrospective study as "research not involving human subjects."

Inclusion criteria

All eligible adult inpatients 18 years old to 87 years old at Hartford Hospital within the period of June 2013 to June 2015 were selected. Patients were included if they received were on therapeutic anticoagulation (defined as a dose >80 mg daily, i.e., at least two doses of daily enoxaparin) for inpatient for the treatment of DVT or PE. Only a patient's first visit with an order for at least two enoxaparin doses was considered.

Exclusion criteria

Patients were excluded if they were greater than 88 years (because of the risk of patient identity issues), or never admitted to the inpatient unit, or had received enoxaparin treatment for anything other than VTE or PE, or for VTE or PE prophylaxis only. Patients were also excluded if they had received inconsistent dosing schedules including patients who received only one treatment dose, patients who received the first dose in the emergency department. Other exclusion criteria, which fell into the abnormal dosing schedule category, were; orders entered into the CPOE system as "now dosing", orders expected to be given at a particular time rather than daily, enoxaparin doses never were given, dosing schedules changing from every 12 h to every 24 h or the reverse and patients who were switched from treatment to prophylaxis then back to treatment doses.

Data collection procedures

Preliminary data were downloaded from the WORx pharmacy management software that handles medications for hospitals and healthcare enterprises. Additionally, from the Sunrise System supplementary data were collected including the time the first order was placed, time of administration for the first dose, time of administration of the second dose, the reason for anticoagulation and number of comorbidities during the stay, not including DVT and or PE. If discharge diagnoses were not reported in the discharge summaries, the number of comorbidities was collected from the problem list. **Appendix 1** (flowchart) summarizes the process of selecting the patients for the study. Based on inclusion and exclusion criteria were applied; a total of 275 patients were eligible for the study.

Study variables

The patient's' demographics included - age in years, gender (male/female), race (white, and Others including African American, Asian, American Indian, Spanish/Hispanic, Other, Pacific Islander/Hawaiian, Unknown). Patients' medical characteristics were the reason for admission/chief complaint, indication for enoxaparin use, medical unit, the number of comorbidities, the admission date, and the discharge date. Enoxaparin dose given in the hospital according to the 1.5 mg/kg/day weight-based dosing was collected. Time difference between order and first dose (TDO1) and time difference between first dose and second dose (TD12) were computed. The difference in admission and discharge dates was calculated to get HospLOS days. However, since patients may have stayed in the hospital before enoxaparin order date, the difference in enoxaparin order date and the discharge date was computed as the hospital adjusted LOS.

To address specific objectives, first descriptive statistics were reported by patient groups based on the TDO1 (≤ 2 h and >2 h) and TD12 (<18 h, 18-24 h and ≥ 25 h). Patient characteristics were described for these groups as proportions for categorical variables, and mean [± standard deviation] and median [25th percentile and 75th percentile] for continuous variables. For inferential statistics, patient groups TDO1 (≤ 2 h and >2 h) and TD12 (<18 h, 18-24 h and ≥ 24 h) were compared for statistically significant differences between patient characteristics (categorical variables; sex, race, service unit) using Wilcoxon-Mann-Whitney test for non-normally distributed data. Patient's medical characteristics (continuous variables: age, comorbidities) were compared using the Spearman Correlation test. Association between continuous independent (time) and dependent (LOS) variables was compared using Spearman Correlation using both as continuous variables and Wilcoxon-Mann-Whitney test using the time-difference variable as a categorical variable. A P value of less than 0.05 was considered significant for all analyses. Statistical analyses were conducted using SAS Version 9.4 (SAS Institute Inc, Cary, North Carolina).

To determine the variations in TDO1, the authors defined the two groups as first treatment dose enoxaparin administered ≤

2 h (TD01 ≤ 2) from the order placement and >2 h from order placement (TD01>2). There have been no set guidelines describing the specific time interval in which patients need to receive anticoagulation by once they are admitted to the hospital. However, the timing of administration within 2 h has been determined by the study hospital's protocol necessitating the nursing staff to administer the medication within 1 h after the pharmacy has prepared the order and giving medicine 1 h to make for the correct dosage of the drug [9]. Study hospital pharmacist' expert opinion stated "if the second dose is given before ¾ of the time interval, it can potentially cause toxicity" [11]. Therefore the categories for the time variable TD12 were set to be the time of the second dose after the first dose; <18, 18-24 and ≥ 25 h, respectively.

RESULTS

Clinically evaluable results were available in 275 patients receiving enoxaparin from June 2013 to June 2015 for DVT, PE or DVT & PE. **Table 1** shows that the most common indication for anticoagulation was DVT treatment (TD01 ≤ 2/>2, 47%/50%; TD12<18/18-24/ ≥ 25 h, 46%/49%/50%), though not statistically significant across the TD01 and TD12 groups, respectively. The median administration times across the TD01 (1.20 vs. 4.76) and TD12 groups (15.58 vs. 22.78 vs. 25.33) were statistically significant (p<0.0001). There were no statistically significant differences in age, gender, race, service area, year, indication or number of comorbidities across each of the TD01 and TD12 groups, respectively.

Table 1. Characteristics of study patients by enoxaparin administration times.

Characteristics (frequency, %; unless otherwise specified*)	Time Difference between Enoxaparin Order and Dose 1 (TD01; hours (h))		Time Difference between Enoxaparin Dose 1 and Dose 2 (TD12; hours (h))		
	<2 (n=115, 42%)	>/=2 (n=160, 58%)	<18 (n=91; 33%)	18-24 (n=169, 61%)	>/=25 (n=15, 5%)
Time Difference*,#	1.20 (0.8, 1.52; 0.03-2.04)	4.76 (2.92, 9.85; 2.05-87.43)	15.58 (13.28, 16.55; 8.48-17.75)	22.78 (21, 23.80; 17.97-24.90)	25.33 (25.23, 26.17; 25.08-32.82)
Enoxaparin Dose*	110 (90, 140; 40-190)	110 (90, 130; 70-270)	110 (90, 130; 70-270)	110 (90, 140;40-200)	110 (80, 120; 70-170)
Age*	65 (54,74; 21-86)	66 (53,77; 18-87)	67 (58,76; 18-87)	64 (52, 75; 21-86)	58 (51, 73; 29-86)
Gender, Male/Female	52 (45 %)/63 (55 %)	79 (49 %)/81 (51 %)	44 (48 %)/47 (52 %)	83 (51 %)/86 (49 %)	4 (27 %)/11 (73 %)
Race, White/Other	81 (70 %)/34 (30 %)	118 (74 %)/42 (26 %)	66 (73 %)/25 (27 %)	123 (73 %)/46 (27 %)	10 (67 %)/5 (33 %)
Comorbidities*	3 (2,5; 0-12)	3 (2,5.5; 0-17)	4 (2,5; 0-12)	3 (2,5; 0-17)	3 (2,5; 0-7)
Service Unit, Medicine/Other	82 (71 %)/33 (29 %)	123 (77 %)/37 (23 %)	74 (81 %)/17 (19 %)	120 (71 %)/49 (29 %)	11 (73 %)/4 (27 %)
Indication					
DVT	54 (47 %)	80 (50 %)	42 (46 %)	83 (49 %)	9 (60 %)
PE	30 (26 %)	49 (31 %)	28 (31 %)	47 (28 %)	4 (27 %)
DVT & PE	31 (27 %)	31 (19 %)	21 (23 %)	39 (23 %)	2 (13 %)

Table 2 shows that the hospital LOS were not significantly different across each of the TD01 (median 6 days in ≤ 2 and >2 h) groups and TD12 (median 6, 6, 5 days in <18, 18-24 and / ≥ 25 h) groups, respectively. The hospital LOSadj each were also not significantly different across each of the TD01 (median 4 days in ≤ 2 and >2 h) groups and TD12 (median 3, 4, 5 days in <18, 18-24 and / ≥ 25 h) groups, respectively. Further, the range of Hospital LOSadj was 1-69 days in the TD01 >2 h patient group and TD12 <18 h patient group.

Table 2. Clinical outcomes of study patients on enoxaparin by enoxaparin administration times.

Outcomes, Median (p25, p75; Range)	Time Difference between Enoxaparin Order & Dose 1 (TD01; hours (h))		Time Difference between Enoxaparin Dose 1 & Dose 2 (TD12; hours (h))		
	<2 (n=115, 42%)	>/=2 (n=160, 58%)	<18 (n=91; 33%)	18-24 (n=169, 61%)	>/=25 (n=15, 5%)
Hospital LOS (days)	6 (4,11; 1-57)	6 (4, 13; 1-93)	6 (4, 11; 1-70)	6 (4, 13; 1-93)	5 (3, 17; 1-27)
Hospital LOS adjusted (days)	4 (2,6; 1-44)	4 (2, 6; 1-69)	3 (2, 5; 1-69)	4 (2,7; 1-52)	5 (3, 9; 1-23)

Note: LOS: Hospital Length of Stay; LOSadj: Hospital Length of Stay Adjusted to Enoxaparin order Placement. #P <0.05 statistically significant

DISCUSSION

VTE remains a significant health care burden in the US, particularly among the elderly, and highlight a continuing increase in the prevalence of the disease [12].The economic impact of increased hospital LOS related to any VTE events has been documented [13].As a result, studies suggest that decreasing the number of days in the hospital decreases hospitalization costs significantly [2]. However, there have been no studies evaluating the associations between the variations in the timing of doses of anticoagulants and the hospital LOS. To the authors' knowledge, this is one of the first studies to evaluate the association between enoxaparin (an anticoagulant), dosing time variations and the LOS in the hospital for patients.

The first finding was that about 42% (119/275) patients received the first enoxaparin treatment dose ≤ 2 h from the order time, while about 52% (163/275) patients received the first enoxaparin treatment dose >2 hours from the order time. Further,

33% (91/275) patients received the second dose <18 h from the first dose. 61% (169/275) received their second dose between 18 to 24 h from the first dose while 5% (15/275) patients received their second dose ≥ 25 h from the first dose. The finding is reported for the first time in the U.S. This is because even though a recent 4 week retrospective pilot study in 67 inpatients showed that enoxaparin dosing and monitoring practices did not match guidelines at an Australian hospital,14 the study did not focus on the timing of administration as in the current study. Time differences in TDO1 and TD12 groups arise from differences in administration of these doses by multiple nurses.

There is more than one nursing staff working at various times throughout the hospital and each nurse works differently, at their pace. Therefore, the administration times are not consistent throughout the study period. Also, none of the patient characteristics (age, inpatient dose, sex, race, service unit, year, comorbidities and indication) were significantly associated with differences among the across each of the TDO1 and TD12 groups respectively **(Table 1).** Reasons for the findings are not known to the authors, as further investigation was beyond the scope of the study. A second important finding reported for the first time was that although the differences were not statistically significant; patients receiving the second dose within 18 h of the first dose had lower median hospital LOSadj (adjusted for enoxaparin dosing) than patients receiving the second dose between 18-24 h or ≥ 25 h, respectively.

The median hospital LOSadj days for TD12 groups <18/18-24/ ≥ 25 h were 3/4/5 respectively. Thus, although non-significant, TD12 ≥ 18 group(s) (18-24 h and ≥ 25 h) had a higher hospital LOSadj days than TD12 <18-hour group. However, the range of hospital LOS adjusted from enoxaparin doing was 1-69 days in TDO1>2 h and TD12<18 h patient groups; though not significantly different across the groups. The finding of a trend of prolonged hospital LOS is similar to the recent 4 week retrospective study at an Australian hospital that also reported: "Although not significant, there was a trend toward noncompliant patients having a greater LOS in the hospital" [14]. However, the current study finding is in the context of the timing of enoxaparin administration compared to the Australian hospital study's 14 contexts of compliance with dosing and monitoring guidelines.

The study has several limitations. First, the authors were unable to study the association between time differences and bleeding events/DVT recurrence because these outcomes were not available in the study data sources. Also, information on whether the patients who received enoxaparin with the varied timing had recurrent VTE or bleeding after they have been discharged from the hospital was not available in the current study. This is because the study focused on one hospitalization and the LOS of that corresponding hospitalization Future evaluations of CPOE systems should consider documentation of such outcomes for monitoring the safety and quality of care in these patients because the immediate outcome of recurrent VTE or bleeding, that can have an effect on the hospital LOS outcome. Second, because of limitations on the availability of immediate outcome data, a surrogate measure of hospital LOS and LOSadj were chosen which also might have affected the study estimates.

The study patients may have developed an acute VTE during their hospital stay and may not have been on enoxaparin treatment since the day of admission. Therefore, to control for such patients, authors used the adjusted hospital LOS to the order date of enoxaparin to the discharge date. However, the hospital LOS measures also have limitations. The study findings may have been affected by hospital LOS measures being rounded to the nearest day because the admit date and discharge date were not recorded with a time of discharge. For example, Patient 1 was admitted on 6/1/2013 at 00:30 AM and was discharged on 6/2/2013 at 23:00 PM after receiving 2 treatment doses of enoxaparin. Patient 2 was admitted on 6/1/2013 at 22:30 PM and was discharged after the 2nd dose the next day, 6/2/2013 at 10:00 AM. Even though patient 2 spent less than 24 h in the hospital, both of the patients had 2 days for the hospital LOS. However, future evaluation can consider the time of discharge; if such data are available to account for the limitations in the hospital LOS measures in the current study.

Third, the study findings may have been affected by other confounders which are not documented in a consistent manner in the databases. Confounders include limb elevation, early ambulation, graduated compression stockings, intermittent pneumatic compression boots, green field filters and inferior vena cava filters. Fourth, the total enoxaparin doses could also have affected study findings because most patients will be getting at least 3 months of therapy for VTE treatment. The prolonged treatment means that enoxaparin doses may have been started or continued before or after their hospital stays. Fifth, being an observational retrospective study, it relied hugely on accurate record keeping. Many of the hospital discharge notes were inconsistent, which may have caused some subjective errors in recordings that cannot be verified by the authors.

Despite the limitations, the authors retrospectively evaluated the study hospital's current electronic computerized ordering/ scheduling system for enoxaparin administration. The finding of significant time differences in administering the first dose after order entry as well as the second dose after the first dose suggest delays in the first dose and earlier second dose in enoxaparin dosing therapy. The findings could help the study hospital determine if the current and future system predispose enoxaparin doses to be given in too short of an interval, leading to patient safety risks or given too late of an interval, leading to sub-optimal clinical efficacy. The study hospital is in the process of implementing electronic medical records (EPIC). Despite the non-significant study findings, the current evaluation provides a baseline methodology and estimates that can be used for designing future such assessments. This new CPOE system may allow for improved adverse effect documentation, such as bleeding events or recurrent DVT. This improvement would allow for future studies on differences in enoxaparin administration (early or delayed) with appropriate outcomes of interest that might potentially give different results. The new CPOE system may also allow the use of the study findings for improved timing through programs that prevent too early or delayed administration of critical medications, such as anticoagulants.

CONCLUSION

Although the variations in enoxaparin administration timing were significant, hospital LOS did not significantly correlate with enoxaparin administration time differences. However, there was a not significant trend toward patients receiving delayed first dose beyond 2 h and earlier second doses within 18 h of the first dose which had a greater range of LOS days in the hospital. Differences in enoxaparin administration times of the first dose from order entry and second dose from the first dose could increase the risk of DVT, PE or both that warrant further attention of hospital providers, policy makers, and future researchers. With the new CPOE system implementation shortly, steps need to be taken to improve documentation adverse events and optimize administration timing of medications in hospitals.

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AUTHOR'S CONTRIBUTION

Concept and design (JS, NT, DH, KL); ethical approval (JS, NT); acquisition of data (NT, DH, KL, JS); study data analyses (JS); interpretation of data (JS, DH, KL); writing and drafting of the initial manuscript (DH, KL) under the supervision of JS; and critical revision of the manuscript for important intellectual content (JS, DH, KL, NT).

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