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Evaluation of a Treatment-Dose Enoxaparin Protocol for Patients With Obesity

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Abstract

Background: Treatment-dose enoxaparin is not well studied in obese patients. Guidelines suggest that obese patients receiving enoxaparin therapy for acute venous thromboembolism (VTE) should receive a standard initial dose, 1 mg/kg, based on actual body weight. It is possible that this dosing strategy in obese patients may be overestimated, leading to a higher bleeding risk compared to non-obese patients. **Objective:** To gather data regarding enoxaparin treatment dosing and anti-Xa level monitoring in patients who are obese to guide dose adjustments. **Methods:** A single-center, retrospective chart review that included patients who were ordered treatment-dose enoxaparin and had a BMI $\geq$ 40 kg/m^2, which resulted in an automatic pharmacy consult. The primary endpoint of this study was incidence of bleeding. **Results:** The analysis included 102 patients. Most patients (92.1%) had a BMI of $\geq$ 40-60 kg/m^2 while 7.8% of patients had a BMI of > 60 kg/m^2. The average initial and final doses were 1.0 $\pm$ 0.1 mg/kg and 0.9 $\pm$ 0.2 mg/kg, respectively. The incidence of bleeding was 4.9%. The average dose for those that bled was 0.7 $\pm$ 0.1 mg/kg. On average, patients who bled had higher BMIs than patients who did not bleed (51.6 kg/m^2 vs. 48.0 kg/m^2). Of the 71 patients with an initial anti-Xa level, 42 of the levels were considered supratherapeutic (59.2%). **Conclusion:** A 1 mg/kg starting dose of enoxaparin may be too high for patients who are obese as many patients required an adjustment to their dose after initial anti-Xa levels.

Keywords

anticoagulation, obesity, enoxaparin

Introduction

Enoxaparin is a low-molecular-weight heparin (LMWH) that is used for a variety of indications such as deep vein thrombosis (DVT) and pulmonary embolism (PE) treatment and prophylaxis. Patients with a high body mass index (BMI) are at risk of being overdosed with treatment-dose enoxaparin due to the uncertainty of pharmacokinetics in these patients.[1] With the incidence of obesity growing to over 39.8% in the United States, hospital admissions of patients with obesity have proportionally increased.[2,3] Patients with high body weights that are receiving enoxaparin are of interest since obesity is an independent risk factor for the development of venous thromboembolism (VTE), however, treatment-dose enoxaparin is not well studied in this patient population.[4,5] Current literature provides conflicting recommendations on enoxaparin treatment dosing and the use of anti-factor Xa (anti-Xa) levels for monitoring in patients with obesity.

In non-obese individuals, enoxaparin has well-defined pharmacokinetics.[4] However, standard enoxaparin doses in patients with high body weights often do not result in therapeutic anti-Xa levels.[6,7] The volume of distribution of enoxaparin is similar to plasma and enoxaparin does not distribute into adipose tissue.[8] Because enoxaparin does not distribute into adipose tissue, it is likely that enoxaparin treatment dosing in patients with high body weights is overestimated, potentially leading to higher than necessary doses, higher anti-Xa levels, and subsequently higher bleeding risks compared to patients who are not obese.[2]

Currently, the standard treatment dose of enoxaparin for VTE is 1 mg/kg twice daily or 1.5 mg/kg once daily and peak anti-Xa levels are the only suggested laboratory test for monitoring safety and efficacy of enoxaparin.[4,6,7,9,10] The American Society of Hematology (ASH) 2018 guidelines suggest that patients with obesity receiving LMWH therapy for acute VTE treatment should receive a standard initial dose based on actual body weight rather than a fixed maximum daily dose.[11] When using

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a dosing regimen that differs from the standard recommended dosing of enoxaparin in patients with high body weights, it is important to consider best monitoring practices to ensure efficacy and safety of treatment. The CHEST guidelines from 2012 suggest monitoring anti-Xa levels in patients with obesity.[7] In comparison, the 2018 ASH guidelines suggest against anti-Xa monitoring as a guide for LMWH dose adjustments.[11] However, this recommendation is noted as having very low certainty in the evidence about the effects for net harm from adjusting LMWH doses based on anti-Xa levels.[11] As noted in the ASH guidelines, anti-Xa test reproducibility is poor, indicating that the resulting anti-Xa measurements may be unreliable, adding to the uncertainty of usefulness.[11] A review by Egan et al concluded that anti-Xa concentration was not strongly associated with clinical outcomes, including thrombosis and hemorrhage, and found no difference in these outcomes between obese and non-obese patients.[4] Utilizing appropriate dosing and monitoring is important when considering the differences between obese and non-obese patients and should take risk factors for thrombosis and bleeding into account.

As mentioned, ASH currently recommends the use of enoxaparin 1 mg/kg twice daily for treatment-dosing in patients with obesity.[11] However, because this can lead to higher than necessary doses and anti-Xa levels of enoxaparin in these patients, it is possible that these patients may need a dose adjustment to prevent an increased bleeding risk. Several recent studies suggest that a dose reduction in patients with morbid obesity will likely result in therapeutic anti-Xa levels without an increased risk of bleeding or VTE.[2,10,12,13] Additional literature also suggests that standard enoxaparin doses in patient with high body weights may lead to supratherapeutic anti-Xa levels, which may put these patients at an increased risk of bleeding.[2,12,14] A retrospective analysis by Sacha et al concluded that patients with obesity achieved therapeutic anti-Xa levels with doses lower than standard doses.[15] A literature review of available data concluded that empiric dose adjustments of approximately 0.7-0.8 mg/kg of actual body weight every 12 hours should be implemented in patients with a BMI $\geq$ 40 kg/m^2 while considering other patient specific risk factors.[1]

The available data and guideline recommendations leads to an unclear answer regarding the most appropriate dosing and monitoring of enoxaparin in this patient population. Therefore, the aim of this study is to add to the literature and provide additional data regarding enoxaparin treatment dosing in patients with obesity and the value of monitoring anti-Xa levels to guide dose adjustments.

Methods

This was a single-center, observational, retrospective chart review that was conducted from April 1, 2018 through August 31, 2019. The local institutional review board approved the study. An electronic data pull was performed to find patients with an order for treatment-dose enoxaparin. Data was collected and managed using REDCap electronic database.[16,17] Patients included had an order for treatment-dose enoxaparin and had a BMI $\geq$ 40 kg/m^2 (per institution protocol). By meeting these 2 criteria, an automatic pharmacy to dose enoxaparin consult is placed. Patients under the age of 18, those with a CrCl < 30 mL/min on day of therapy initiation, receiving hemodialysis, who were pregnant, or who were continued on their home enoxaparin therapy were excluded.

This institution has a pharmacy to dose enoxaparin protocol that allows pharmacists to manage therapeutic enoxaparin dosing when treatment-dose enoxaparin 1 mg/kg subcutaneously (SC) q12 h is ordered for a patient with a BMI $\geq$ 40 kg/m^2. Enoxaparin doses are rounded to the nearest 10 mg. Once a dose is initiated, an anti-Xa level is ordered by the pharmacist to be checked at steady state, 4 hours after the 3rd or 4th dose of enoxaparin. The anti-Xa goal range is 0.5 -1 units/mL, based on the 1 mg/kg SC q12 h dosing. If available, serum creatinine (SCr), blood urea nitrogen (BUN), hemoglobin (Hgb), and platelets are reviewed in order to assess renal function and potential safety concerns. For levels outside of the therapeutic range, doses are adjusted based upon a chart adapted from the 2001 CHEST guidelines.[18] Levels may be checked earlier if patient status warrants. Generally, once a patient is on a stable on a dose of enoxaparin, anti-Xa levels are assessed weekly.

The primary objective of this study was to evaluate the safety of enoxaparin dosing in patients with a BMI $\geq$ 40 kg/m^2 by determining the incidence of bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH).[19] Secondary objectives were to identify the incidence of thromboembolic events, identify instances where pharmacists used clinical judgement to adjust a dose based on patient specific factors, and to determine the correlation between anti-Xa levels with safety and efficacy outcomes.Major bleeding was defined 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 and/or bleeding causing a fall in hemoglobin level of 2 g/dL or more leading to a transfusion of two or more units of whole blood or red cells.[19] Bleeding was assessed during enoxaparin therapy and up to 24 hours after discontinuation of enoxaparin treatment. If enoxaparin was held for more than 24 hours and then a bleeding event occurred, bleeding was deemed not to be related to enoxaparin therapy.[20]

Secondary endpoints evaluated include number and severity of bleeding events, development of a new thromboembolic event, average mg/kg enoxaparin dose, initial anti-Xa level, average anti-Xa level at the time of bleed (if a bleed occurred), average number of anti-Xa levels drawn per patient, and average number of anti-Xa levels drawn prior to achieving a therapeutic level. The average mg/kg dose was analyzed in all included patients.

Statistical Methods

The sample size was estimated to be approximately 125 patients. The sample size analysis was based on the margin of error for estimating the primary outcome, incidence of

bleeding, in the study population. Assuming a 1-4% incidence of bleeding, based on a review of the literature, a sample size of 125 would allow estimation of the incidence of bleeding to within 3.5%, with 95% confidence. The sample size analysis was performed using PASS 15 Power Analysis and Sample Size Software (2017). Our actual sample size of 102 fell short of the anticipated number. Rather than perform a post hoc sample size analysis, we assessed the precision of our estimate for the incidence of bleeding by calculating an exact 95% confidence interval. The data was analyzed using descriptive statistics, including means and standard deviations for interval data, and counts and percentages for categorical data. Statistical results were generated using SAS Enterprise Guide 7.1.

Results

A total of 150 patients who received treatment-dose enoxaparin were screened for inclusion. Of these 150 patients, the final analysis included 102 patients. 48 patients were excluded based on pre-determined exclusion criteria.Patient demographics and clinical characteristics were collected and analyzed (Table 1). Of the 102 patients included, 92.1% of patients had a BMI of $\geq$ 40 - 60 kg/m^2 while 7.8% of patients had a BMI of > 60 kg/m^2. Thirty-six patients were on a concomitant antiplatelet (19.6%), warfarin (14.7%), or DOAC (1.0%). Of the included patients, 67.7% of patients were on enoxaparin for the treatment of VTE.

The primary endpoint, incidence of bleeding, occurred in 4.9% (5/102) of patients with a 95% CI of 1.6-11.1% (Table 2). Of the 5 patients that experienced bleeding, 3 bleeds were considered major, based on the pre-determined definition of bleeding.[19] Of the major bleeds, 2 out of 3 received blood products. The average initial enoxaparin dose was 1.0 $\pm$ 0.1 mg/kg and the average final dose was 0.9 $\pm$ 0.2 mg/kg (Table 3).The average enoxaparin dose for the patients that experienced a bleed was 0.7 $\pm$ 0.1 mg/kg (Table 2). The average anti-Xa level closest to time of bleed was 0.7 $\pm$ 0.5, noting that only 3/5 patients had an anti-Xa level drawn. On average, patients who bled had a higher BMI than patients who did not bleed (51.6 kg/m^2 vs. 48.0 kg/m^2) (Table 4). The incidence of thrombosis was 0.9% (1/102) of patients (Table 5). The enoxaparin dose for this patient was 1.0 mg/kg.

Thirty-one patients did not have an anti-Xa level recorded. Of the 71 patients who had an initial anti-Xa level recorded, 42 of the levels were considered supratherapeutic (59.2%) (Table 6). An average of 2.6 anti-Xa levels were drawn per patient and an average of 1.1 anti-Xa levels were drawn prior to achieving a therapeutic anti-Xa result.

Table 1. Patient Demographics and Clinical Characteristics (n = 102)[a].

Patient characteristics	n (%)
Gender	
Female	71 (69.6)
Male	31 (30.4)
Age (years)	
Mean $\pm$ SD	55.7
Median	57.0
Range	20.0 – 80.0
Race	
White	53 (54.6)
Black or African American	40 (41.2)
American Indian or Alaska Native	3 (3.1)
Asian	1 (1.0)
Unknown	5 (4.9)
Body Mass Index (BMI)	
$\geq$40-60 kg/m^2	94 (92.1)
>60 kg/m^2	8 (7.8)
Total Body Weight (TBW) (kg)	
Mean $\pm$ SD	137.6 $\pm$ 27.5
Ideal Body Weight (IBW) (kg)	
Mean $\pm$ SD	61.7 $\pm$ 10.5
Adjusted Body Weight (AjBW) (kg)	
Mean $\pm$ SD	92.8 $\pm$ 17.6
Cancer	
No active disease	81 (79.4)
Active disease	21 (20.6)
Primary Service	
Medicine	54 (67.5)
Hematology/Oncology	13 (16.3)
Surgery	7 (8.8)
Trauma	6 (7.5)
Other	22 (21.6)
Recent Surgery[b]	
Yes	29 (28.4)
No	73 (71.6)
Concomitant Medications	
Antiplatelets	20 (19.6)
Warfarin	15 (14.7)
DOAC	1 (1.0)
NSAIDs	0
Recent Bleeding[c]	
Yes	10 (9.8)
No	92 (90.2)
Blood Products Received	
Yes	2 (2.0)
No	100 (98.0)
Enoxaparin Treatment Indication	
VTE (DVT/PE)	69 (67.7)
Stroke Prevention for Non-Valvular Atrial Fibrillation	19 (18.6)
Other	14 (13.7)

[a]NSAID = non-steroidal anti-inflammatory drug, DOAC = direct oral anticoagulant
[b]Major surgical procedure or trauma within 30 days before start of therapy
[c]Recent GI bleed (within the last 6 months), any history of intracranial, intraocular, spinal, or intra-articular hemorrhage

Discussion

Enoxaparin dosing in patients who are obese is not well-defined and evidence for the most appropriate dosing and monitoring is limited. Based on the enoxaparin doses collected, the average final enoxaparin doses for those experiencing a bleed was 0.7 $\pm$ 0.1 mg/kg. This finding indicates that the standard recommended 1 mg/kg dosing for treatment-dose enoxaparin may be too high of an initial dose for patients with high body weights. However, it is possible that these patients may have had an intrinsically higher risk of bleeding that was not dose

Table 2. Bleeding Outcomes.

Incidence of bleeding, n (%)	5 (4.9), CI (1.6% - 11.1%)
Average anti-Xa level at time of bleed, mean ± SD	0.7 ± 0.5[a]
Major	3 (60.0)
Minor	2 (40.0)
Dosing in patients who experienced bleeding, mg/kg, mean ± SD	0.7 ± 0.1

[a]3 levels recorded

Table 3. Average Enoxaparin Treatment Doses (mg/kg).

Average dose (mg/kg)	Mean ± SD
Initial dose	1.0 ± 0.1
Final dose (when therapeutic anti-Xa level results)	0.9 ± 0.2
Patients who did not develop a subsequent clot or experience bleeding (n = 96)	
mg/kg	0.9 ± 0.2
% of patients	94.1

Table 4. Dose Comparisons.

	Patients who bled (mean ± SD)	Patients who did not bleed (mean ± SD)
BMI (kg/m^2)	51.6 ± 6.6	48.0 ± 8.5
Initial enoxaparin dose (mg/kg)	0.9 ± 0.1	1.0 ± 0.1
Enoxaparin dose (final) (mg/kg)	0.7 ± 0.1	0.9 ± 0.2
Initial anti-Xa level drawn (units/mL)	1.3 ± 0.1	1.1 ± 0.4
Final anti-Xa level drawn (closest to bleeding or final dose) (units/mL)	0.7 ± 0.5	1.0 ± 0.4
Average # of anti-Xa levels drawn	2.0 ± 0.8	2.6 ± 2.0

Table 5. Thrombosis Outcomes.

Incidence of thrombosis, n (%)	1 (1.0)
Average anti-Xa level at time of thrombosis, mean ± SD	Not available
Dosing in patients who developed a subsequent clot (mg/kg)	1.0

Table 6. Effect of Enoxaparin Dosing Regimens on Initial Anti-Xa levels[a].

Anti-Xa levels (units/mL)	Frequency, n (%)
Subtherapeutic (<0.5)	4 (5.6)
Therapeutic (0.5 -1)	25 (35.2)
Supratherapeutic (>1)	42 (59.2)

[a]31 patients did not have an anti-X[a] recorded

dependent. Another finding of this study was that the patients who bled had, on average, a higher BMI and initial anti-Xa level. Based on their BMIs, these patients would likely have been receiving larger doses of enoxaparin. This would in turn put them at an increased risk of bleeding, which may have been associated with the higher anti-Xa levels. However, a correlation between anti-Xa levels and bleeding was not able to be assessed due to sample size.

On average, the final doses of enoxaparin were lower than the initial doses, which indicates that starting at a lower dose may prevent adverse events, such as bleeding, in patients who are obese. However, the data from this analysis is not strong enough to make this conclusion based on sample size and incidence of bleeding. It is important to note that a large portion (39.2%) of patients required a dose adjustment based on respective anti-Xa levels. Regarding anti-Xa levels, of the 71 patients who had an initial anti-Xa level recorded, 42 (59.2%) of those levels were supratherapeutic. This is another indicator that standard enoxaparin dosing may be too high in patients with obesity.

When compared to other studies, our initial anti-Xa level distributions were similar. Of the patients enrolled in a study by Deal et al,[12] which used the same definition of obesity, 40% of patients with supratherapeutic anti-Xa levels experienced bleeding, whereas none of the patients who had a therapeutic anti-Xa level experienced bleeding. Those findings indicate that there is likely a correlation between supratherapeutic anti-Xa levels and bleeding, which is important to consider in patients with high body weights who are typically getting large doses of enoxaparin. In a study by Lalama et al[10] enoxaparin doses were automatically adjusted to 0.75 mg/kg every 12 hours if the patient had a BMI over 40 kg/m^2. This resulted in 77.4% of patients achieving therapeutic anti-Xa levels during their hospitalization and may correlate to the low incidence of bleeding and thrombotic events found in that study.[10]

This study has several limitations. The small percent of patients who bled did not allow for evaluation of statistical significance between the two groups. Additionally, the definition of obesity used differs from other relevant literature and supportive guidelines.Using a BMI $\geq$ 40 kg/m^2 allowed us to include patients who were at highest risk for receiving larger doses of enoxaparin that may lead to bleeding. In general, there is a paucity of information on how to adjust enoxaparin doses based upon anti-Xa levels. The chart our institution uses was adapted from the 2001 CHEST Guidelines and contains anti-Xa level ranges, provides guidance on whether the next dose of enoxaparin should be held, percent of dosage change indicated, and when to check subsequent anti-Xa levels based on the change made.[18] While this is the best guidance we have at this time, there is a lack of data supporting its use in the adult population as it was initially developed for pediatric patients. Lastly, there was no comparison to non-obese patients to determine differences in incidence of bleeding and final enoxaparin doses, so we were not able to make conclusions about differences between these two populations. A study by Hagopian et al[20] compared patients with high body weights (BMI $\geq$ 40 kg/m^2) to patients with a BMI $<$ 40 kg/m^2 and found no difference in bleeding or thromboembolic events, however dose capping at enoxaparin 150 mg was utilized in the morbidly obese group.

As discussed, given the small sample size analyzed in this study, a final conclusion on an appropriate starting dose for treatment-dose enoxaparin in patients with obesity cannot be

determined. Future studies should incorporate a comparison group of non-obese patients at the same institution to determine if there are differences regarding initial anti-Xa levels and incidence of bleeding. Additionally, a randomized controlled trial in patients with high body weights would be beneficial to determine the most appropriate enoxaparin dose for this patient population. Based on the current information available from this study and previously mentioned studies, it is important to recognize that patients with obesity likely require lower starting doses of enoxaparin to reduce the risk of bleeding.

Conclusion

In conclusion, the results of this study are suggestive that a 1 mg/kg starting dose may be too high for patients who are obese. The patients who experienced bleeding (4.9%) had, on average, higher BMIs than those who did not bleed and many patients required an adjustment to their enoxaparin dose after initial anti-Xa levels were obtained. However, the data in this analysis does not allow for a conclusion to be drawn about the most appropriate starting dose for treatment-dose enoxaparin in patients with high body weights, which indicates a need for additional studies in the future.

Declaration of Conflicting Interests

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References

1. Sebaaly J, Covert K. Enoxaparin dosing at extremes of weight: literature review and dosing recommendations. *Ann Pharmacother.* 2018: 52(9);898-909.
2. Thompson-Moore NR, Wanat MA, Putney DR, et al. Evaluation of the pharmacokinetics of treatment dose enoxaparin in hospitalized patients with morbid obesity. *Clin Appl ThrombHemost*. 2015; 21(6):513-520.
3. Hales CM, Carroll MD, Fryar CD, et al. *Prevalence of Obesity among Adults and Youth: United States, 2015–2016. NCHS Data Brief, no 288*. National Center for Health Statistics; 2017.
4. Egan G, Ensom MH. Measuring anti-factor Xa activity to monitor low-molecular-weight heparin in obesity: a critical review. *Can J Hosp Pharm*. 2015;68(1):33-47.
5. Samama M, for the Sirius Study Group. An epidemiologic study of risk factors for deep vein thrombosis in medical outpatients: The Sirius Study. *Arch Intern Med*. 2000;160(22):3415-3420. doi:10.1001/archinte.160.22.3415
6. Tahaineh L, Edaily S, Gharaibeh S. Anti-factor Xa levels in obese patients receiving enoxaparin for treatment and prophylaxis indications. *Clin Pharmacol.* 2018:10;63-70. (took out of intro, not sure if used elsewhere, need to check)
7. Garica DA, Baglin TP, Weitz JI, et al. Parenteral anticoagulants: antithrombotic therapy and prevention of thrombosis, 9th ed: American college of chest physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2 suppl): e24S-e43S. doi:10.1378/chest.11-2291
8. Sanderink G, Le Liboux A, Jariwala N, et al. The pharmacokinetics and pharmacodynamics of enoxaparin in obese volunteers. *Clin Pharmacol Ther*. 2002;72(3):308-318. doi:10.1067/mcp.2002.127114
9. Lovenox [package insert]. Sanofi-Aventis; 2018.
10. Lalama JR, Feeney ME, Vandiver JW, et al. Assessing an enoxaparin dosing protocol in morbidly obese patients. *J Thromb Thrombolysis*. 2015; 39(4):516-521.
11. Witt D, Nieuwlaat R, Clark N, et al. American society of hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. *Blood*. 2018; 2(22):3257-3291.
12. Deal EN, Hollands JM, Riney JN, et al. Evaluation of therapeutic anticoagulation with enoxaparin and associated anti-Xa monitoring in patients with morbid obesity: a case series. *J Thromb Thrombolysis*. 2011;32(2):188-194.
13. Spinler SA, Ou FS, Roe MT, et al. Weight-based dosing of enoxaparin in obese patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSAD initiative. *Pharmacotherapy*. 2009; 29(6):631-638. doi: 10.1592/phco.29.6.631.
14. Lee YR, Vega JA, Duong HN, et al. Monitoring enoxaparin with anti-factor Xa levels in obese patients. *Pharmacotherapy*. 2015; 35(11):1007-1015.
15. Sacha GL, Greenlee KM, Ketz JM. The use of anti-factor Xa monitoring in a selection of patients receiving enoxaparin at a large academic medical center. *J Thromb Thrombolysis*. 2016; 42(6):479-485.
16. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support, *J Biomed Inform*. 2009;42(2):377-381.
17. Harris PA, Taylor R, Minor BL, et al. REDCap Consortium, The REDCap consortium: Building an international community of software partners. *J Biomed Inform*. 2019;95:103208. doi:10.1016/j.jbi.2019.103208
18. Monagle P, Michelson AD, Bovill E, et al. Antithrombotic therapy in children. *Chest*. 2001;119(1 Suppl): S344-S370.
19. Schulman S, Kearon C on behalf of the subcommittee on control of anticoagulation of the Scientific and Standardization committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb-Haemost*. 2005;3(4):692-694.
20. Hagopian JC, Riney JN, Hollands JM, et al. Assessment of bleeding events associated with short-duration therapeutic enoxaparin used in the morbidly obese. *Ann Pharmacother*. 2013;47(12): 1641-1648.