Admission thrombelastography does not guide dose adjustment of enoxaparin in trauma patients

Hannah V. Hayes, MD [a,*], Molly E. Droege, PharmD, BCPS [b,c], Craig J. Furnish, PharmD [d], Michael D. Goodman, MD, FACS [a], Neil E. Ernst, PharmD [b,c], Christopher A. Droege, PharmD, BCCCP, FCCM [b,c]

[a] University of Cincinnati Department of Surgery, Cincinnati, OH
[b] UC Health–University of Cincinnati Medical Center Department of Pharmacy, Cincinnati, OH
[c] University of Cincinnati James L. Winkle College of Pharmacy, Division of Pharmacy Practice and Administrative Sciences, Cincinnati, OH
[d] University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences, Aurora, CO

ARTICLE INFO

ABSTRACT

Background: Enoxaparin is used as chemoprophylaxis to reduce incidence of venous thromboembolism and its complications following trauma. Serum anti-Xa monitoring is used to assess efficacy but requires several doses to be administered. Thrombelastography assesses hypercoagulability and may have utility identifying high-risk patients for venous thromboembolism. The objective was to evaluate whether thrombelastography parameters could identify trauma patients requiring enoxaparin dose adjustment earlier than serum anti-Xa concentrations.
Methods: A single-center, retrospective medical record review evaluated patients admitted to a regional level I trauma center that received an admission thrombelastography and a dose of enoxaparin with a serum trough anti-Xa concentration drawn. Patients were divided into standard-dose or dose-adjusted enoxaparin. Venous thromboembolism incidence between groups and risk factors for enoxaparin dose adjustment and venous thromboembolism development were evaluated.
Results: A total of 204 patients were included. Differences observed between groups included age (standard-dose enoxaparin, 48.5 [29.3–72] vs dose-adjusted enoxaparin, 38.5 [25–55.7] years; $P = .005$), admission creatinine clearance (standard-dose enoxaparin, 92.9 [67.4–113.4] vs dose-adjusted enoxaparin, 102.1 [83.8–129.2] mL/min; $P = .017$), and time to venous thromboembolism prophylaxis initiation (standard-dose enoxaparin, 23.8 [11.2–36.4] vs dose-adjusted enoxaparin, 34.5 [18.3–52.7] hours; $P = .004$). No differences in thrombelastography parameters or venous thromboembolism incidence were observed. No independent risk factors for enoxaparin dose adjustment were identified; however, risk assessment profile score > 10 was an independent risk factor for venous thromboembolism development.
Conclusion: No relationship between admission thrombelastography and need for enoxaparin dose adjustment in trauma patients was observed. As thrombelastography continues growing in clinical use, it is prudent to investigate other potential applications. Currently, thrombelastography should not be used to guide enoxaparin dosing.
© 2020 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

BACKGROUND

Venous thromboembolism (VTE) is a significant source of morbidity and mortality in traumatically injured patients [1]. The interplay of Virchow's triad (ie, hemostasis or alteration of blood flow, endothelial injury, hypercoagulability) is often the underlying mechanism that results in development of VTE [2]. Derangements in clotting factors can occur, which produce a hypercoagulable response contributing to the formation of a thrombus [3–5]. The incidence of VTE ranges from 5% to 31% in the intensive care unit, and 25%–38% of trauma patients are hypercoagulable upon arrival to the emergency department [6–8].

Thrombelastography (TEG) is tool to measure the viscoelastic clotting properties of blood. TEG parameters have been used as a rapid predictor of 24-hour mortality, and its usefulness in guiding blood transfusions has been well documented [9–11]. Components of the clotting cascade are broken down into 5 parameters that can be interpreted to determine the ability of the blood to form a clot: clot formation (R time), speed of clot amplification (K time and α angle), clot strength (maximum amplitude [MA]), and how quickly the clot degrades (percent lysis at 30 minutes [LY30]). These values can provide an accurate representation of underlying coagulopathy or hypercoagulability present within a patient. Individually, these components may pinpoint specific deficiencies present in the coagulation cascade [12].

* Corresponding author at: Department of Surgery, University of Cincinnati, 231 Albert Sabin Way, ML 0558, Cincinnati, OH 45267. Tel.:+ 1 513 546 4144; fax:+ 1 513 558 3474.
E-mail address: lewishv@ucmail.uc.edu (H.V. Hayes).

VTE chemoprophylaxis should be considered in trauma patients as soon as clinically appropriate and continued through the admission [13]. Guidelines suggest utilization of low–molecular weight heparins (LMWHs), such as enoxaparin, as the prophylactic agent of choice for prevention of VTE [14,15]. Traditionally, the criterion standard for monitoring LMWH efficacy is the serum anti-Xa (aXa) concentration [16,17]. However, recent studies have questioned if aXa monitoring is the most optimal laboratory value to determine if the dose of enoxaparin is adequate. These studies have failed to show a significant association between enoxaparin dose and aXa activity after initiation of prophylaxis but have suggested a positive association between enoxaparin and TEGR time [18,19]. Trials have investigated TEG-guided enoxaparin dosing after initiation of prophylaxis but have been unable to correlate TEG parameters with dose adjustment after therapy initiation [19]. The ability to use an admission TEG, prior to prophylaxis initiation, to identify patients needing a dose adjustment sooner could potentially decrease VTE incidence because it is believed that earlier initiation of an appropriately dosed LMWH along with diligent continuation of administration may help to prevent VTE [20]. Our hypothesis was that an admission TEG could predict need for dose adjustment of enoxaparin in patients presenting with trauma. Secondary aims looked at VTE incidence, time to chemoprophylaxis initiation, and risk factors for enoxaparin dose adjustment and for VTE development.

METHODS

Data Collection. This single-center, retrospective medical record review of trauma patients was approved by the Institutional Review Board of the University of Cincinnati. Data were extracted from the trauma registry and the electronic health record at the University of Cincinnati Medical Center, a regional academic medical and level I trauma center. The trauma registry contains patient demographic and baseline characteristics (eg, age, weight, sex, ethnicity, race), VTE occurrence and type, comorbidities, initial VTE prophylaxis agent (ie, LMWH, subcutaneous heparin), dose of VTE prophylaxis agent, time to VTE prophylaxis administration from admission, TEG parameters, blood products received (in units), injury severity score (ISS), abbreviated injury severity, risk assessment profile score (RAP), injury type (ie, blunt, penetrating), admission creatinine, and patient outcome (ie, alive, deceased). This database was queried for patients meeting prespecified inclusion criteria, which are defined below. Patients in the database were evaluated for inclusion in the review.

Patients were eligible for inclusion in the review if they received an admission rapid TEG in the emergency department and received a dose of enoxaparin with serum trough aXa drawn before the fourth dose to assess for presence of active drug providing prophylaxis. Patients were excluded if they were <18 years of age, were pregnant, were prisoners, had a creatinine clearance < 30 mL/min, or had evidence of 1 or more missed or held doses of enoxaparin during admission. Patients were then stratified into dose-adjusted (DAE) or standard-dose enoxaparin (SDE) groups based on dose administered. All patients initially received a dose of enoxaparin at 30 mg twice daily (BID) subcutaneously (SQ) or 40 mg BID SQ based upon weight (patients with an actual body weight < 125 kg or body mass index < 40 received 30 mg BIDSQ, patients with an actual body weight ≥ 125 kg or body mass index ≥ 40 received 40 mg BID SQ). An aXa level was then drawn within 1 hour prior to the fourth dose, if the aXa level was detectable (≥0.1 IU/mL), they were maintained at their inital dose. If aXa was undetectable (<0.1 IU/mL), their dose was increased to 40 mg BID SQ or 50 mg BIDSQ,based on their weight, per University of Cincinnati Medical Center trauma service protocol (Supplemental Figure). SDE was defined as patients being maintained on the dose of 30 mg BID SQ or 40 mg BID SQ based on weight. DAE was defined as requiring a dose adjustment after aXa level with the adjusted dose being 40 mg BID SQ or 50 mg BID SQ based on weight.

VTE was defined as deep venous thromboembolism or pulmonary embolism as documented in the medical record or evidenced by

increase to therapeutic dosing of enoxaparin. Those patients who were determined to be high risk for VTE via a RAPscore ≥ 5 received a bilateral screening lower extremity venous duplex ultrasound within the first 4 days after admission and then weekly while hospitalized. Venous duplex ultrasounds were also performed if the patients exhibited any pain in a limb, swelling in a limb, edema, unspecified respiratory abnormality, or unspecified chest pain. Patients who were identified to have an above-the-kneeVTE were treated with therapeutic anticoagulation, whereas patients identified to have a distal VTE (below the knee) were continued on their chemoprophylactic enoxaparin dose and the duplex repeated in 1 week to assess for propagation to a proximal VTE.

Data Analysis. A post hoc analysis of the data was conducted once all study participants were identified. All continuous variables were compared using a Student t test or Mann-Whitney U, whereas categorical variables were compared via χ^2 or Fisher exact test, as appropriate. Univariate analyses were performed to assess for associations with the need for enoxaparin dose adjustment and VTE development. Multivariate logistic regression analyses were performed with all covariates with P value < .2 from the corresponding univariate analysis to identify independent risk factors for need for dose adjustment or VTE development. The authors reserved the right to force in variables into the multivariate analysis that they believed might have affected the outcome. All statistical analyses were performed using SigmaPlot 11 software (Systat, San Jose, CA).

RESULTS

A total of 204 (64 SDE, 140 DAE) patients met inclusion criteria within the trauma registry. Characteristics between groups were similar except for age (median [interquartile range]: SDE, 48.5 [29.3–72] vs DAE, 38.5 [25.0–55.7] years; $P = .005$), admission creatinine clearance (SDE, 92.9 [67.4–113.4] vs DAE, 102.1 [83.8–129.2] mL/min; $P = .017$), and time to VTE prophylaxis (SDE, 23.8 [11.2–36.4] vs DAE, 34.5 [18.3–52.7] hours; $P = .004$) (Table1). No differences were observed between TEG parameters between patients in SDE and DAE groups (Table2).

Twenty-seven patients developed a VTE. Baseline characteristics were similar between groups except for RAP score (VTE, 12 [9–14] vs no VTE, 8 [6–10]; $P < .001$), time to VTE prophylaxis initiation (VTE, 42.1 [18.2–65.9] vs no VTE, 27.8 [16.0–44.0] hours; $P = .027$), and packed red blood cells (pRBC) (VTE, 1 [0–4] vs no VTE, 0 [0–1]; $P = .002$) and fresh frozen plasma (FFP) (VTE, 1 [0–4] vs no VTE 0 [0–1]; $P = .005$) received in the first 24 hours. No differences were observed in TEG parameters between groups (Table3).

Factors considered for the need for enoxaparin dose adjustment in addition to age and admission creatinine clearance included admission K time (SDE, 82.5 [70–93.75] vs DAE, 85.0 [65.0–115] seconds), admission MA (SDE, 63.6 [58.9–66.6] vs DAE, 62.2 [56.3–65.5]), admission

Table 1
Baseline characteristics dose-adjusted versus standard-dose groups

Characteristic	Dose adjusted (n = 140)	Standard dose (n = 64)	P value
Age, y	38.5 (25–55.8)	48.5 (29.3–72.0)	.005
RAP score	8 (6–12)	9 (7–11.3)	.312
Male, n (%)	105 (68.6)	35 (68.6)	.682
Weight, kg	87.6 (72.3–105.1)	81.9 (72.3–98.6)	.535
Admission CrCl, mL/min	102.1 (83.8–129.2)	92.9 (67.4–113.4)	.017
Blunt, n (%)	109 (77.9)	52 (81.3)	.714
ISS	22 (14.5–29.0)	20 (14.5–26.8)	.178
Time to VTE ppx initiation, h	34.49 (18.28–52.66)	23.79 (11.22–36.38)	.004
pRBC, U/24 h	0 (0–2)	0 (0–1)	.402
FFP, U/24 h	0 (0–1)	0 (0–1)	.810

All data represented as median (interquartile range) unless otherwise specified.
CrCl, creatinine clearance; *ppx*, prophylaxis.

Table 2
TEG values of dose-adjusted versus standard-dose groups

TEG value	Dose adjusted (n = 140)	Standard dose (n = 64)	P value
R time, s	45 (35–55)	40 (35–50)	.370
K time, s	85 (65–115)	82.5 (70–93.8)	.138
Angle, °	75 (71.4–77.9)	75.9 (74–77.4)	.171
MA, mm	62.2 (56.3–65.5)	63.6 (58.9–66.6)	.062
LY30, m	1.15 (0.13–2.98)	1.2 (0.13–3.1)	.904
ACT, s	121 (105–136)	113 (105–128)	.413

All data represented as median (interquartile range).
ACT, activating clotting time.

angle (SDE, 75.9° [74.0°–77.4°] vs DAE, 75.0° [71.4°–77.9°]), ISS (SDE, 20 [14.5–26.8] vs DAE, 22 [14.5–29.0]), and MA:*R* ratio (SDE, 1.59 [1.18–1.87] vs DAE, 1.43 [1.06–1.80]). No independent risk factors were identified on multivariate logistic regression for the need for enoxaparin dose adjustment.

Factors associated with VTE development included age (VTE, 53 [29–65] vs no VTE, 41 [25.5–57.5] years), RAP score (VTE, 12 [9–14] vs no VTE, 8 [6–10]), time to VTE prophylaxis (VTE, 42.1 [18.2–65.9] vs no VTE, 27.8 [16.0–44.0] hours), weight (VTE, 88.7 [76.5–109.3] vs no VTE, 84.2 [72.0–103.4] kg), pRBC (VTE, 1 [0–4] vs no VTE, 0 [0–1] units) and FFP (VTE, 1 [0–4] vs no VTE, 0 [0–1] U). The RAP score (odds ratio 1.20 [95% confidence interval 1.065–1.354]; *P* = .003) was the only independent predictor for VTE development (Table 4).

DISCUSSION

This single center, medical record–based review explored whether TEG values obtained for trauma patients upon admission could predict the need for an enoxaparin dose adjustment during hospital stay. No individual TEG parameters were significantly different between SDE and DAE groups. Multivariate regressions failed to show any correlation with a need for enoxaparin dose adjustment; however, a RAP score > 10 correlated with increased risk of VTE occurrence, which supports findings from previous studies [21,22]. Although ISS did not meet the criteria for *P* < .2, it was forced in because previous studies have shown that patients with higher ISS have a higher risk of VTE [23]. However, our study failed to show an association between ISS and increased VTE incidence on multivariate analysis. Other studies have explored the relation of *R* time and LMWH dose increases but have not been able to show statistical differences in rates of VTE between study groups [18,19,24]. To date, no study has been able to demonstrate improvements in VTE rates using TEG values to adjust LMWH dosing.

Our study reviewed 204 patients admitted to a trauma service at a large academic medical center who received an admission TEG and enoxaparin at any point during their hospitalization with serum aXa trough drawn. Patients overall were generally younger (<50 years of age), suffered blunt trauma, and had ISS scores that were categorized as moderate to severe injury. There were significant differences between the SDE and DAE groups at baseline, including age, admission creatinine clearance, and time to VTE prophylaxis initiation. Generally, younger patients required dose adjustments of enoxaparin, which can be attributed to faster metabolism, higher volume of distribution for water-soluble drugs, and fewer comorbidities [25,26]. Additionally, in

Table 3
TEG values of VTE versus no-VTE groups

TEG value	VTE (n = 27)	No VTE (n = 177)	P value
R time, s	40 (30–55)	40 (35–55)	.786
K time, s	80 (67.5–115)	85 (65–115)	.911
Angle, °	75.4 (72.6–77.5)	75.2 (72.1–77.8)	.813
MA, mm	62.4 (57.7–66.9)	62.5 (56.6–65.9)	.766
LY30, m	1.5 (0.3–4.3)	1.2 (0.1–3.0)	.764
ACT, s	113 (97–136)	113 (105–136)	.819

All data represented as median (interquartile range).

Table 4
Multivariate analysis for risk factors of VTE development

Characteristic	Odds ratio (95% CI)	P value
Age, y	1.02 (0.996–1.05)	.101
RAP score	1.17 (1.02–1.35)	.027
Weight, kg	1.01 (0.992–1.03)	.242
ISS	1.01 (0.960–1.05)	.839
Time to VTE, ppx, h	1.02 (0.997–1.03)	.097
pRBC, U/24 h	1.05 (0.757–1.44)	.789
FFP, U/24 h	1.01 (0.735–1.40)	.932

Hosmer-Lemeshow *P* = .790.

the DAE group, creatinine clearance was noted to be significantly higher. Other studies have noted this and suggested that those with higher creatinine clearance could exhibit faster drug elimination, resulting in lower levels of aXa activity; therefore, they would require dose adjustment to attain adequate levels [27]. Median time to VTE prophylaxis initiation differed by approximately 12 hours, which also represents the duration of activity of one 40-mg dose of enoxaparin [28]. This reinforces previous research indicating that timely initiation of VTE prophylaxis is imperative to decrease the incidence of VTE, as well as consistent administration of prophylaxis with minimization of missed doses [[29],30].

Our univariate analysis is consistent with much of the literature available to date in that no TEG parameters seem to individually predict the need for an enoxaparin dose adjustment. The benefit of correlating such a finding would have prevented patients from receiving subtherapeutic dosing of LMWH much earlier than the traditional 3 or 4 doses of enoxaparin that must be administered prior to drawing a serum aXa trough level after 36–48 hours. Although previous data have revealed that higher admission MA values (eg, MA > 65 mm, MA > 72 mm) were predictive of increased risk of pulmonary embolism, our study found no significant difference between MA value and VTE incidence [31]. There have also been studies investigating the MA/*R* ratio, where lower MA/*R* ratios have indicated a higher mortality, yet our data showed no significance between lower MA/*R* ratios and higher mortality [32]. Additional research on the utility of MA as clinical marker for LMWH dose adjustment is required to further investigate these findings.

There are several limitations to our study that must be addressed. The retrospective review limits the amount of control on extemporaneous factors that may impact a patient's need for dose adjustment. Lack of standardization of timing of VTE prophylaxis initiation could significantly impact the incidence of VTE between the 2 groups. It is possible that not all patients with VTE were captured because only patients with RAP > 5 were screened using lower extremity duplex sonography. However, as the observed median RAP for patients with VTE and without VTE was 12 (9–14) and 8 (6–10), respectively, greater than 75% of patients in both groups received duplex scans per protocol, and we believe the small amount of patients that did not receive duplex scans would not affect the outcome of the study. This should minimize, but not eliminate, the observational bias of the VTE outcome. Additionally, using a post hoc analysis allows the possibility of investigator bias of the results. Furthermore, being a single-site study with convenience size sampling limits the external validity of our study. Finally, smaller sample size led to significant differences in baseline characteristics that may have impacted outcomes of interest.

In conclusion, this study sought to explore if TEG parameters obtained on admission could guide enoxaparin dosing during the inpatient stay, with the intention of being able to recognize the need for dose adjustment sooner than the current criterion standard test, aXa. Unfortunately, we found no TEG parameter predicted need for enoxaparin dose adjustment; however, this study highlighted that physiologic criteria, including creatinine clearance, continue to be better predictors of chemoprophylaxis pharmacodynamics and the RAP score continues to correlate with VTE risk in the trauma patient population. As TEG

continues to gain popularity in clinical use, it is prudent to explore other potential applications to the data it provides. Given the limitations of our study, future larger, multi-institutional studies could potentially further elucidate the role TEG may play in dosing enoxaparin; however, at this time, TEG should not be used to guide enoxaparin dosing.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sopen.2020.03.003.

Author Contribution

MED, CJF, CAD, NEE, and MDG were involved in the conception and design of the study. MED, CJF, CAD, NEE, and MDG were involved in acquisition of data. MED, CJF, and CAD were involved in data analysis and interpretation. HVH, CJF, and CAD drafted the manuscript, and all authors contributed to the revision of the manuscript for publication. HVH presented this research at the 14th Annual Academic Surgical Congress in Houston, TX.

Conflict of Interest

The authors report no conflict of interest regarding proprietary or commercial interest in any product mentioned or concept discussed in this article.

Funding Sources

References

[1] Meizoso JP, Karcutskie CA, Ray JJ, Ruiz X, Ginzburg E, Namias N, et al. A simplified stratification system for venous thromboembolism risk in severely injured patients. J Surg Res 2017 Jan;207:138–44. https://doi.org/10.1016/j.jss.2016.08.072.

[2] Rogers FB. Venous thromboembolism in trauma patients: a review. Surgery. 2001 Jan;130(1): 1–12. https://doi.org/10.1067/msy.2001.114558.

[3] Harr JN, Moore EE, Wohlauer MV, Droz N, Fragoso M, Banerjee A, et al. The acute coagulopathy of trauma is due to impaired initial thrombin generation but not clot formation or clot strength. J Surg Res 2011 Oct;170(2):319–24. https://doi.org/10.1016/j.jss.2011.03.047 [Epub 2011 Apr 17].

[4] Maegele M, Schöchl H, Cohen MJ. An update on the coagulopathy of trauma. Shock 2014 May;41(Suppl. 1):21–5. https://doi.org/10.1097/SHK.0000000000000088.

[5] Mammen EF. Pathogenesis of venous thrombosis. Chest 1992 Dec;102(6): 640S–644S. https://doi.org/10.1378/chest.102.6_Supplement.640S.

[6] Minet C, Potton A, Hamidfar-Roy R, Somohano CS, Lugosi M, Cartier JC, et al. Venous thromboembolism in the ICU: main characteristics, diagnosis and thromboprophylaxis. Crit Care 2015 Aug 18;19:287. https://doi.org/10.1186/s13054-015-1003-9.

[7] Brown LM, Aro SO, Cohen MJ. Trauma Outcomes Group, Holcomb JB, Wade CE et al. A high fresh frozen plasma: packed red blood cell transfusion ratio decreases mortality in all massively transfused trauma patients regardless of admission international normalized ratio. J Trauma 2011 Aug;71(2 Suppl 3):S358–63. https://doi.org/10.1097/TA.0b013e318227f152.

[8] Branco BC, Inaba K, Ives C, Okoye O, Shulman I, David JS, et al. Thromboelastogram evaluation of the impact of hypercoagulability in trauma patients. Shock 2014 Mar;41(3):200–7. https://doi.org/10.1097/SHK.0000000000000109.

[9] Einersen PM, Moore EE, Chapman MP, Moore HB, Gonzalez E, Silliman CC, et al. Rapid thrombelastography thresholds for goal-directed resuscitation of patients at risk for massive transfusion. J Trauma Acute Care Surg 2017 Jan;82(1):114–9. https://doi.org/10.1097/TA.0000000000001270.

[10] Tapia NM, Chang A, Norman M, Welsh F, Scott B, Wall Jr MJ, et al. TEG-guided resuscitation is superior to standardized MTP resuscitation in massively transfused penetrating trauma patients. J Trauma Acute Care Surg 2013 Feb;74(2):378–85. https://doi.org/10.1097/TA.0b013e31827e20e0.

[11] Hampton DA, Lee TH, Diggs BS, McCully SP, Schreiber MA. A predictive model of early mortality in trauma patients. Am J Surg 2014 May;207(5):642–7 discussion 647 https://doi.org/10.1016/j.amjsurg.2013.12.009. [Epub 2014 Jan 31].

[12] Salooja N, Perry DJ. Thrombelastography. Blood Coagul Fibrinolysis 2001 Jul;12(5): 327–37. https://doi.org/10.1097/00001721-200107000-00001.

[13] Bryne JP, Mason SA, Gomez D, Hoeft C, Subacius H, Xiong W, et al. Timing of pharmacologic venous thromboembolism prophylaxis in severe traumatic brain injury: a propensity-matched cohort study. J Am Coll Surg. 2016 Oct;223(4):621–631.e5. doi: https://doi.org/10.1016/j.jamcollsurg.2016.06.382. [Epub 2016 Jul 21].

[14] Rogers FB, Cipolle MD, Velmahos G, Rozycki G, Luchette FA. Practice management guidelines for the prevention of venous thromboembolism in trauma patients: the EAST practice management guidelines work group. J Trauma 2002 Jul;53(1): 142–64.

[15] Geerts WH, Jay RM, Code KI, Chen E, Szalai JP, SaibiL EA et al. A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboembolism after major trauma. N Engl J Med. 1996 Sep;5:335(10):701–7. DOI: https://doi.org/10.1056/NEJM199609053351003

[16] Babin JL, Traylor KL, Witt DM. Laboratory monitoring of low-molecular-weight heparin and fondaparinux. Semin Thromb Hemost 2017 Apr;43(3):261–9. https://doi.org/10.1055/s-0036-1581129 [Epub 2016 Jun 9].

[17] Singer GA, Riggi G, Karcutskie CA, et al. Anti–Xa–guided enoxaparin thromboprophylaxis reduces rate of deep venous thromboembolism in high risk trauma patients. J Trauma Acute Care Surg 2016 Dec;81(6):1101–8. https://doi.org/10.1097/TA.0000000000001193.

[18] Van PY, Cho SD, Underwood SJ, Morris MS, Watters JM, Schreiber MA. Thrombelastography versus antifactor Xa levels in the assessment of prophylactic-dose enoxaparin in critically ill patients. J Trauma 2009 Jun;66(6):1509–15 discussion 1515-7 https://doi.org/10.1097/TA.0b013e3181a51e33.

[19] Louis SG, Van PY, Riha GM, Barton JS, Kunio NR, Underwood SJ, et al. Thromboelastogram-guided enoxaparin dosing does not confer protection from deep venous thrombosis: a randomized controlled pilot trial. J Trauma Acute Care Surg 2014 Apr;76(4):937–42 discussion 942-3 https://doi.org/10.1097/TA.0000000000000165.

[20] Connelly CR, Van PY, Hart KD, Louis SG, Fair KA, Erickson AS, et al. Thromboelastography-based dosing of enoxaparin for thromboprophylaxis in trauma and surgical patients: a randomized clinical trial. JAMA Surg 2016 Oct;151(10): e162069. https://doi.org/10.1001/jamasurg.2016.2069 [Epub 2016 Oct 19].

[21] Greenfield LJ, Proctor MC, Rodriguez JL, Luchetter FA, Cipolle MD, Cho J. Posttrauma thromboembolism prophylaxis. J Trauma. 1997 Jan;42(1):100–3. doi:10.1097%2F00005373–199701000-00017.

[22] Gearhart MM, Luchette FA, Proctor MC, Lutomski DM, Witsken C, James L, et al. The risk assessment profile score identifies trauma patients at risk for deep vein thrombosis. Surgery 2000 Oct;128(4):631–40. https://doi.org/10.1067/msy.2000.108224.

[23] Dennis JW, Menawat S, Von Thron J, Fallon Jr WF, Vinsant GO, Laneve LM, et al. Efficacy of deep venous thrombosis prophylaxis in trauma patients and identification of high risk groups. J Trauma 1992 Jul;35(1):132–8 [discussion 138-9].

[24] Harr JN, Moore EE, Chin TL, Ghasabyan A, Gonzalez E, Wohlauer MV, et al. Platelets are dominant contributors to hypercoagulability after injury. J Trauma Acute Care Surg 2013 Mar;74(3):756–62 discussion 762-5 https://doi.org/10.1097/TA.0b013e3182826d7e.

[25] Fung LS, Klockau C. Effects of age and weight-based dosing of enoxaparin on anti–factor Xa levels in pediatric patients. J Pediatr Pharmacol Ther 2010 Apr;15(2): 119–25.

[26] Mangoni AA, Jackson SHD. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. Br J Clin Pharmacol 2004 Jan; 57(1):6–14. https://doi.org/10.1046/j.1365-2125.2003.02007.x.

[27] Ko A, Harada MY, Barmparas G, Chung K, Mason R, Yim DA, et al. Association between enoxaparin dosage adjusted by anti–factor Xa trough level and clinically evident venous thromboembolism after trauma. JAMA Surg 2016 Nov;151(11): 1006–13. https://doi.org/10.1001/jamasurg.2016.1662.

[28] Enoxaparin. Lexi-Drugs. Lexicomp-Online. Hudson, Ohio; Lexicomp Inc: 2007. Updated 4/1/17. Accessed 4/3/18.

[29] Nathens AB, McMurray MK, Cuschieri J, Durr EA, Moore EE, Bankey PE, et al. The practice of venous thromboembolism prophylaxis in the major trauma patient. J Trauma 2007 Mar;63(3):557–63. https://doi.org/10.1097/TA.0b013e318031b5f5.

[30] Louis SG, Sato M, Geraci T, Anderson R, Cho SD, Van PY, et al. Correlation of missed doses of enoxaparin with increased incidence of deep vein thrombosis in trauma and general surgery patients. JAMA Surg 2014 Apr;149(4):365–70. https://doi.org/10.1001/jamasurg.2013.3963.

[31] Cotton BA, Minei KM, Radwan ZA, Matijevic N, Pivalizza E, Podbielski J, et al. Admission rapid thrombelastography predicts development of pulmonary embolism in trauma patients. J Trauma Acute Care Surg 2012 Jun;72(6):1470–7 discussion 1475-7 https://doi.org/10.1097/TA.0b013e31824d56ad.

[32] Savage SA, Zarzaur BL, Pohlman TH, Brewer BL, Magnotti LJ, Croce MA, et al. Clot dynamics and mortality: the MA-R ratio. J Trauma Acute Care Surg 2017 Oct;83(4): 628–34. https://doi.org/10.1097/TA.0000000000001637.