Identification of hypercoagulability with thrombelastography in patients with hip fracture receiving thromboprophylaxis

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Background: Venous thromboembolism (VTE) is the second most common complication after hip fracture surgery. We used thrombelastography (TEG), a whole-blood, point-of-care test that can provide an overview of the clotting process, to determine the duration of hypercoagulability after hip fracture surgery.

Methods: In this prospective study, consecutive patients aged 51 years or more with hip fractures (trochanteric region or neck) amenable to surgical treatment who presented to the emergency department were eligible for enrolment. Thrombelastography, including calculation of the coagulation index (CI) (combination of 4 TEG parameters for an overall assessment of coagulation) was performed daily from admission until 5 days postoperatively, and at 2 and 6 weeks postoperatively. All patients received 28 days of thromboprophylaxis. We used single-sample *t* tests to compare mean maximal amplitude (MA) values (a measure of clot strength) to the hypercoagulable threshold of greater than 65 mm, a predictor of in-hospital VTE.

Results: Of the 35 patients enrolled, 11 (31%) were hypercoagulable on admission based on an MA value greater than 65 mm, and 29 (83%) were hypercoagulable based on a CI value greater than 3.0; the corresponding values at 6 weeks were 23 (66%) and 34 (97%). All patients had an MA value greater than 65 mm at 2 weeks. Patients demonstrated normal coagulation on admission (mean MA value 62.2 mm [standard deviation (SD) 6.3 mm], $p = 0.01$) but became significantly hypercoagulable at 2 weeks (mean 71.6 mm [SD 2.6 mm], $p < 0.001$). There was a trend toward persistent hypercoagulability at 6 weeks (mean MA value 66.2 mm [SD 3.8 mm], $p = 0.06$).

Conclusion: More than 50% of patients remained hypercoagulable 6 weeks after fracture despite thromboprophylaxis. Thrombelastography MA thresholds or a change in MA over time may help predict VTE risk; however, further study is needed.

Contexte : La thromboembolie veineuse (TEV) est la deuxième complication la plus courante après une chirurgie pour fracture de la hanche. Nous avons eu recours à la thromboélastographie, un test de sang total effectué au point d'intervention et donnant une idée du processus de coagulation, pour évaluer la durée de l'hypercoagulabilité à la suite d'une chirurgie pour fracture de la hanche.

Méthodes : Cette étude prospective a été menée auprès de patients consécutifs admissibles de 51 ans et plus qui se sont présentés à l'urgence pour une fracture de la hanche (région trochantérienne ou col du fémur) pouvant faire l'objet d'un traitement chirurgical. Une thromboélastographie (TEG), qui comprenait le calcul de l'indice de coagulation (IC) [combinaison de 4 paramètres du TEG permettant une évaluation globale de la coagulation], a été réalisée chaque jour, de l'admission au cinquième jour postopératoire, de même qu'à 2 et à 6 semaines postopératoires. Tous les patients ont suivi une thromboprophylaxie de 28 jours. Nous avons réalisé des tests *t* pour échantillon unique afin de comparer l'amplitude maximale (AM) moyenne (une mesure de la résistance d'un caillot) au seuil d'hypercoagulabilité de plus de 65 mm, un prédicteur de TEV à l'hôpital.

Résultats : Des 35 patients recrutés, 11 (31 %) présentaient une hypercoagulabilité à l'admission selon une AM supérieure à 65 mm, et 29 (83 %) présentaient une hypercoagulabilité selon un IC supérieur à 3,0; les valeurs correspondantes à 6 semaines étaient de 23 (66 %) et de 34 (97 %), respectivement. Tous les patients avaient une AM de plus de 65 mm à 2 semaines. Dans l'ensemble, les patients avaient une coagulation normale à l'admission (AM moyenne 62,2 mm [écart type (E.T.) 6,3 mm], $p = 0,01$), mais présentaient une hypercoagulabilité importante à 2 semaines (moyenne 71,6 mm [E.T. 2,6 mm], $p < 0,001$). L'hypercoagulabilité avait tendance à persister à 6 semaines (AM moyenne 66,2 mm [E.T. 3,8 mm], $p = 0,06$).

Conclusion : Malgré la thromboprophylaxie, plus de 50 % des patients présentaient toujours une hypercoagulabilité 6 semaines après leur fracture. Les seuils d'AM à la thromboélastographie et les changements de l'AM au fil du temps pourraient aider à prédire le risque de TEV, mais d'autres études sur le sujet sont nécessaires.

Venous thromboembolism (VTE), which comprises deep vein thrombosis or pulmonary embolism, is one of the major causes of morbidity and mortality after hip fracture, and the VTE risk after hip fracture surgery is among the highest of all surgical specialties.[1,2] Venous thromboembolism is the second most common complication after surgery, and pulmonary embolism is the fourth most common cause of death after a hip fracture.[3] Thromboprophylaxis reduces the risk of VTE after hip fracture; however, the optimal duration of anticoagulation is unknown.[1,2,4,5] Extended use of thromboprophylaxis is recommended after hip fracture surgery, but consensus guidelines vary in the recommended duration (10–35 d) and type of anticoagulation.[1,6–8] The benefits of thromboprophylaxis for more than 10 days need to be balanced against associated risks, including bleeding, wound complications and, less commonly, heparin-induced thrombocytopenia.[9] Although clinical practice guidelines can help guide thromboprophylaxis use after surgery, an individualized patient-specific approach could lead to improved outcomes.

Thrombelastography (TEG) is a whole-blood point-of-care test capable of providing clinicians with a global assessment of the clotting process, from fibrin formation to clot lysis, in the form of a graphic tracing.[10,11] Currently, the primary clinical application of TEG is to assess hemostatic defects in bleeding patients to guide resuscitation with blood products.[10,12] Thrombelastography has been shown to detect hypercoagulable states and can predict VTE in patients with orthopedic trauma.[13,14] Two TEG parameters for evaluating hypercoagulability are maximal amplitude (MA) and coagulation index (CI).[15–18]

The objective of this study was to use serial TEG analysis to determine the duration of hypercoagulability after hip fracture surgery. In addition, we aimed to evaluate the utility of the previously determined MA and CI thresholds to define the duration of hypercoagulability after hip fracture surgery.

Methods

Patients

Research ethics board approval was obtained for this prospective cohort study. Consecutive patients aged 51 years or older with hip fractures (AO 31-A1–A3 [trochanteric region] or 31-B1–B3 [neck]) amenable to surgical treatment who presented to our institution's emergency department between Dec. 20, 2017, and Sept. 28, 2018, were eligible for enrolment into the study. Patient consent was obtained before the first blood draw and within 16 hours of the time of hip fracture. Surrogate consent from a legally authorized health care representative was required to enroll patients unable to sign consent at the time of presentation. All patients received surgical treatment for their hip fracture within 48 hours after admission, as per institutional standard of care.

Patients were excluded if they presented to the emergency department more than 16 hours after the injury; had a known bleeding disorder or inherited thrombophilia; had active malignant disease, defined as being diagnosed within 6 months of presentation, having recurrent, regionally advanced metastatic disease, having received treatment within 6 months before study onset, or having hematologic malignant disease not in complete remission; had had anticoagulation therapy before the injury, with the exception of a single-agent antiplatelet medication; had a pathologic hip fracture; or had a periprosthetic hip fracture.

Blood collection and laboratory testing

Whole-blood TEG was performed after emergency department diagnosis of hip fracture, every 24 hours from the time of injury until 5 days postoperatively, and at 2 and 6 weeks. All analyses were done with the TEG 6s hemostasis analyzer (Haemonetics). Patient blood was collected in 2.7 mL tubes containing 3.2% buffered sodium citrate solution and transported to the orthopedic trauma research laboratory. About 0.4 mL of whole blood was manually pipetted into the TEG 6s cartridge entry port for analysis. All tests were performed within 4 hours of blood draw, as recommended by the manufacturer. The members of our orthopedic trauma research team were trained in using the TEG 6s system and performed all tests.

Measures of hypercoagulability

Thrombelastography measures several clotting parameters, including R time (R), K value (K), α-angle and MA. To determine whether a patient was in a hypercoagulable state, we used MA and CI thresholds for hypercoagulability determined a priori.[16–18] The CI formula combines 4 TEG parameters for an overall assessment of coagulation (CI = 0.1227[R] + 0.0092[K] + 0.1655[MA] – 0.0241[α-angle] – 5.0220). R represents clot initiation, measuring the time for enzymatic clotting initiation to reach 2 mm of clot strength. K, α-angle and MA collectively represent clot propagation, measuring the time it takes for the forming clot to reach

20 mm of clot strength, the velocity of clot generation and the maximal platelet–fibrin clot size, respectively.

Normal CI values range from –3.0 to 3.0; values less than –3.0 are considered hypocoagulable, and those greater than 3.0 are considered hypercoagulable.[16] Two MA thresholds have been determined to be independent predictors of in-hospital VTE in patients with trauma: values greater than 65 mm (odds ratio 3.7) (associated with nearly a fourfold increased symptomatic VTE risk) and values greater than 72 mm (odds ratio 6.7); the latter represents greater VTE risk.[17,18] We used the value of greater than 65 mm to define hypercoagulability in our cohort but also report patients with values greater than 72 mm.

Statistical analysis

We summarized baseline demographic data using means with standard deviation (SD), medians with interquartile range (IQR) or frequencies with proportions, as appropriate. All statistical tests were 2-sided, and p values < 0.05 were considered statistically significant. We used 1-sided t tests to compare the mean MA values to the threshold of greater than 65 mm. We compared the association between known risk factors for VTE (increased age and body mass index, female sex) and dichotomous MA values (> 65 mm and ≤ 65 mm) at the 2-week and 6-week follow-up using the χ^2 test for sex and the Wilcoxon rank sum test for age and body mass index. We used R version 3.5.1 (R Foundation for Statistical Computing) for analysis.

Results

Thirty-five consecutive patients with hip fractures were enrolled. The median age was 83 years, and most patients were female (26 [74%]), within normal body mass index (median 23.7) and White (33 [94%]) (Table 1). The majority of patients (31 [89%]) had known medical conditions at the time of hip fracture, with cardiovascular disease (24 [69%]) and osteoporosis (13 [37%]) being the most common. More than one-third of patients (13/34 [38%]) had required ambulatory aids before their hip fracture.

Table 1. Demographic and baseline characteristics

Characteristic	No. (%) of patients* n = 35
Age, median (IQR), yr	83 (71–86)
Female sex	26 (74)
Body mass index, median (IQR) (n = 33)	23.7 (20.6–26.8)
White	33 (94)
Comorbidities	
Diabetes	3 (9)
Cardiovascular disease	24 (69)
Pulmonary disease	9 (26)
History of cancer	5 (14)
Osteoporosis	13 (37)
Smoking status	
Current smoker	4 (11)
Past smoker	14 (40)
Never smoked	17 (49)
Pre-injury level of mobility	
Independent ambulator	21 (62)
Cane	4 (12)
Walker	9 (26)
Missing	1 (3)

IQR = interquartile range.
*Except where noted otherwise.

Table 2. Mean coagulation index values on admission and at 2 and 6 weeks

Time	Mean	Minimum	Maximum
Admission	3.6	–0.03	4.8
2 wk (n = 34)	5.0	4.3	5.9
6 wk	4.2	2.6	5.0

Table 3. Frequency of meeting threshold values for hypercoagulability on admission and at 2 and 6 weeks

	Parameter; no. (%) of patients		
Time	MA > 65 mm	MA > 72 mm	CI > 3.0
Admission	11 (31)	0 (0)	29 (83)
2 wk (n = 34)	34 (100)	16 (47)	34 (100)
6 wk	23 (66)	0 (0)	34 (97)

CI = coagulation index; MA = maximal amplitude.

Measures of hypercoagulability

The mean CI on admission was 3.6, indicating that patients were in a hypercoagulable state after traumatic hip fracture (Table 2). Hypercoagulability persisted at 2 weeks (mean CI 5.0) and 6 weeks (mean CI 4.2). On admission, 11 patients (31%) were in a hypercoagulable state as determined by an MA value greater than 65 mm, compared to 29 patients (83%) based on the CI value (Table 3). At 2 weeks, all patients were in a hypercoagulable state based on an MA value greater than 65 mm and the CI value. Sixteen patients (47%) had an MA value greater than 72 mm at 2 weeks, which suggests that they may have been even more hypercoagulable.[18] At 6 weeks, two-thirds of patients (23 [66%]) were hypercoagulable based on an MA value greater than 65 mm, compared to 34 patients (97%) based on the CI value. All 16 patients with an MA value greater than 72 mm at 2 weeks had values of 65 mm or less by 6 weeks. One patient, a previously healthy 65-year-old woman with no known risk factors for VTE, was diagnosed with symptomatic deep vein thrombosis 3 weeks after hip fracture. At 2 weeks, she was in a hypercoagulable state (MA 77.9 mm, CI 5.9).

When we used the MA threshold of greater than 65 mm to assess hypercoagulability, the patients' mean coagulation status was normal at the time of admission (MA 62.2 mm

[SD 6.3 mm], $p = 0.01$) and on postoperative day 1 (MA 64.0 mm [SD 4.8 mm], $p = 0.3$) (Figure 1). However, patients subsequently became hypercoagulable on postoperative day 3 (mean MA 67.4 mm [SD 4.2 mm], $p = 0.003$). Not only did patients remain hypercoagulable on postoperative day 5 (mean MA 69.6 mm [SD 2.6 mm], $p < 0.001$) and at 2 weeks (mean MA 71.6 mm [SD 2.6 mm], $p < 0.001$), but the mean MA continued to rise during this time. There was a nonsignificant trend toward hypercoagulability that persisted at 6 weeks (mean MA 66.2 mm [SD 3.8 mm], $p = 0.06$).

There was no difference in sex, age or body mass index between patients with MA values greater than 65 mm and those with MA values of 65 mm or less at 2 weeks or 6 weeks (Table 4).

Discussion

In this study using serial TEG analysis to evaluate hypercoagulability following both femoral neck and intertrochanteric hip fractures from the time of admission until 6 weeks postoperatively, more than 50% of patients remained hypercoagulable (MA > 65 mm) 6 weeks after fracture, despite extended-duration thromboprophylaxis.[1,7,8] To our knowledge, only 1 previously published study followed patients with hip fracture serially with TEG.[15] However, only those with femoral neck fractures were recruited, and thromboprophylaxis with enoxaparin, 20 mg/d, was administered for only 7 days postoperatively or until discharge.[15] In

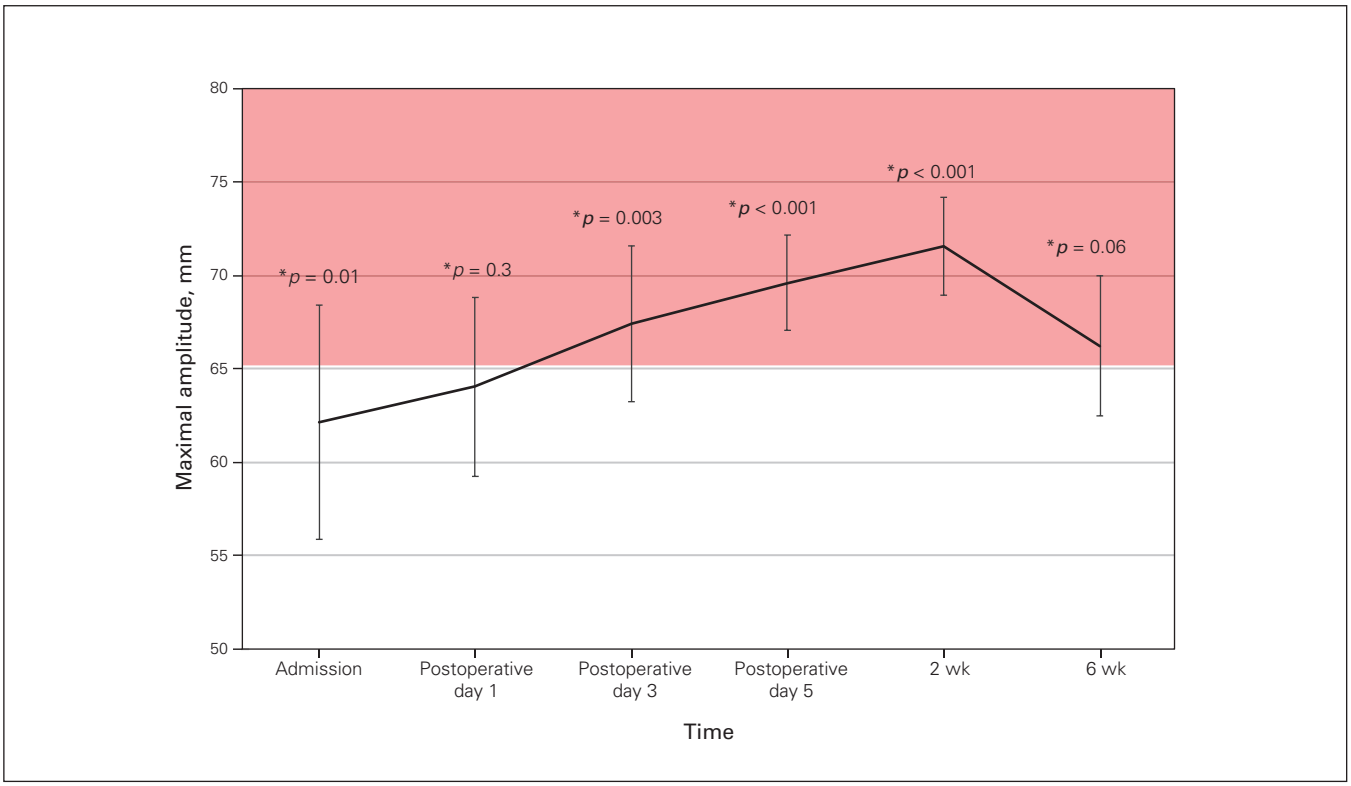

Fig. 1 Mean maximal amplitude (MA) values on admission and over the study period. Error bars represent standard deviation. *One-sided *t* tests comparing mean MA values to the threshold of greater than 65 mm (shaded area), which has been described as an independent predictor of in-hospital pulmonary embolism.[17,18]

Table 4. Association of female sex, age and body mass index with maximal amplitude at 2 and 6 weeks

	2 wk			6 wk		
Variable	MA > 65 mm $n = 16$	MA ≤ 65 mm $n = 18$	*p* value	MA > 65 mm $n = 23$	MA ≤ 65 mm $n = 12$	*p* value
Female sex, no. (%)	11 (69)	15 (83)	0.4*	18 (78)	8 (67)	0.7*
Age, median (IQR), yr	83 (74–87)	85 (71–85)	0.8†	84 (76–87)	74 (66–85)	0.2†
Body mass index, median (IQR)	24.2 (20.7–26.8)	22.5 (20.1–26.8)	0.8†	23.7 (20.9–26.6) $n = 22$	22.8 (19.0–26.9)	0.5†

IQR = interquartile range; MA = maximal amplitude.
*χ^2 test.
†Wilcoxon rank sum test.

addition, the first TEG analysis did not take place until immediately before surgery.[15]

Owing to the inflammatory response after the trauma of a hip fracture, higher circulating levels of inflammatory cytokines activate the coagulation system and inhibit fibrinolysis and anticoagulant pathways, thus increasing the risk of VTE.[19–21] Elevated admission MA has been shown to be an independent predictor for in-hospital pulmonary embolism in patients with trauma.[17,18] Using serial TEG analysis, we quantified a steady increase in MA, which peaked 2 weeks after hip fracture. This finding supports current guideline recommendations for a minimum of 14 days of thromboprophylaxis after hip fracture.[1,7,8] However, 66% of patients remained hypercoagulable at 6 weeks, which is after thromboprophylaxis is typically stopped. Some patients with hip fracture are at risk for VTE as long as 3 months after injury.[2] Identification of these patients so that they may receive a longer duration of thromboprophylaxis may be possible with TEG.

We used previously determined MA and CI thresholds to assess hypercoagulability after hip fracture.[16–18] The CI is believed to be an accurate measurement of the coagulation profile because it considers the enzymatic aspects of clotting by taking into account the R and α-angle.[22] It has been shown to detect hypercoagulability and predict VTE in gynecologic and neurosurgery patients and those with orthopedic trauma.[13–16,22,23] In our cohort, a high proportion of patients (≥ 83%) had a CI value greater than 3.0 on admission, and at 2 and 6 weeks. Previously determined MA thresholds for hypercoagulability may stratify patients' VTE risk better than the CI threshold. In the current study, 31% of patients had an MA value greater than 65 mm on admission, and none had a value greater than 72 mm. Our patients had normal admission MA (mean 62.2 mm), similar to that reported by Gary and colleagues[17] (62 mm). However, the low-energy mechanism of injury involved in geriatric hip fractures is different from that in the high-energy blunt trauma population studied by those authors. Whereas mean time to VTE in the studies by Gary and colleagues[17] and Cotton and colleagues[18] was 5.5 and 8.3 days respectively, older patients with hip fracture may have a prolonged hypercoagulable period, as 32.9% of VTE events occur in the second and third months after injury.[2,17,18] This suggests the utility of performing serial TEG analysis beyond 6 weeks after hip fracture surgery to determine the duration of individual hypercoagulability, as 66% of patients in our study remained in a hypercoagulable state at 6 weeks as determined by an MA value greater than 65 mm. Furthermore, TEG thresholds for hypercoagulability need to be reevaluated in the geriatric population to determine specific values for VTE risk. This would allow for potential risk modification by adjusting thromboprophylaxis dosages or using additional antithrombotic medications known to affect TEG parameters.[24,25]

Increased age and body mass index and female sex, which are factors known to be associated with increased risk for VTE,[26,27] were not found to be associated with hypercoagulable TEG values in our cohort at 2 and 6 weeks. This was likely due to the small sample size. Individual hypercoagulable responses after hip fracture, as shown by TEG, could be incorporated into a future VTE risk prediction model to improve current risk prediction scores, because currently there is no optimal model to predict VTE risk after hip fracture surgery.[27] We plan to study a larger cohort to further elucidate risk factors that can be used in combination with TEG analysis for risk stratification.

This study provides support for assessing rapid increases in MA (or δ MA) with the use of serial TEG analysis, as this may better predict VTE risk. The patient in our cohort who developed symptomatic deep vein thrombosis had an admission MA value of 61.5 mm; however, she had a substantial increase in MA between postoperative day 2 (52.6 mm) and postoperative day 3 (70.5 mm), and her highest measured value was at 2 weeks (77.9 mm). Deep vein thrombosis had been diagnosed in the emergency department 23 days after hip fracture while the patient was receiving thromboprophylaxis; it was treated with rivaroxaban. This case further supports that there are individual hypercoagulable responses after orthopedic trauma.

Limitations

Strengths of our study include prospective collection of data in a population at high risk for VTE, inclusion of patients with delirium or dementia, and demonstration of duration of hypercoagulability by serial TEG measurements. The main limitation is that the thromboprophylaxis regimen was not standardized but, rather, was left to the discretion of the treating surgeon. Medications including warfarin, low-molecular-weight heparin and direct orally administered anticoagulants have been shown to affect the TEG tracing, most notably R.[25,28,29] In our cohort, all patients received thromboprophylaxis as per Thrombosis Canada guidelines,[8] with a minimum duration of 28 days of anticoagulation. Our centre has since standardized chemoprophylaxis for patients with fracture for future studies.

Conclusion

Thrombelastography showed that more than 50% of patients with hip fracture remained hypercoagulable 6 weeks after fracture despite thromboprophylaxis. However, the trend toward hypercoagulability at 6 weeks was nonsignificant, which suggests that hypercoagulability varied according to individual patients. Thrombelastography has the potential to provide clinicians with real-time VTE risk stratification in patients at high risk and to strengthen

current clinical practice guidelines. Further study is required to validate the utility of specific TEG measures of hypercoagulability in a larger cohort of patients with hip fracture as well as in other orthopedic patients, such as those with trauma.

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Contributors: All authors designed the study. D. You and P. Schneider acquired the data, which D. You, L. Skeith, R. Korley, A. Soo and P. Schneider analyzed. D. You and P. Schneider wrote the manuscript, which all authors critically revised. All authors gave final approval of the article to be published.

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