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Higher coagulation activity in hip fracture patients: A case-control study using rotational thromboelastometry

Andreas G. Tsantes[1] | Ioannis G. Trikoupis[2] | Dimitrios V. Papadopoulos[3] | Konstantina A. Tsante[4] | Andreas F. Mavrogenis[2] | Panagiotis Koulouvaris[2] | Olga D. Savvidou[2] | Vasilios A. Kontogeorgakos[2] | Daniele Piovani[5,6] | Anastasios G. Kriebardis[4] | Stefanos Bonovas[5,6] | Panayiotis J. Papagelopoulos[2] | Argirios E. Tsantes[1]

[1]Laboratory of Haematology and Blood Bank Unit, "Attiko" Hospital, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece

[2]First Department of Orthopaedics, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece

[3]Department of Orthopaedic Surgery, University of Pittsburgh, Orthopedic Specialists-UPMC, Pittsburgh, PA, USA

[4]Laboratory of Reliability and Quality Control in Laboratory Hematology (HemQcR), Department of Biomedical Sciences, School of Health & Caring Sciences, University of West Attica (UniWA), Egaleo, Greece

[5]Department of Biomedical Sciences, Humanitas University, Milan, Italy

[6]Humanitas Clinical and Research Center-IRCCS, Milan, Italy

Correspondence
Andreas G. Tsantes, Laboratory of Haematology and Blood Bank Unit, "Attiko" Hospital, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece.
Email: andreas.tsantes@yahoo.com

Abstract

Introduction: Trauma-induced coagulopathy has been extensively investigated in the multitrauma setting, but only sparsely following moderate orthopedic trauma. The purpose of this study was to evaluate changes in the hemostatic profile of patients with hip fractures, using rotational thromboelastometry (ROTEM).

Methods: 198 patients with hip fractures who underwent surgery were included in the study. A matched group of 52 healthy individuals was also enrolled. Demographics, conventional laboratory assays, and ROTEM parameters were recorded and compared between patients and healthy adults. The preoperative and postoperative ROTEM values of fractured patients were also compared.

Results: The conventional coagulation assays were similar for the 2 groups. However, several ROTEM parameters including EXTEM MCF ($P < .001$), EXTEM alpha angle ($P < .001$), INTEM MCF ($P < .001$), INTEM A10 ($P < .001$), and INTEM alpha angle ($P < .001$) significantly differed between the 2 groups indicating a higher coagulation potential following hip fractures. Also, fractured patients had significantly lower INTEM and EXTEM CT values ($P = .008$ and $P = .012$, respectively) and significantly lower INTEM and EXTEM CFT values ($P < .001$). Adjusted analysis for confounders further confirmed the direct relationship between hip fracture and higher coagulation activity. Last, INTEM CT and CFT significantly decreased ($P = .008$ and $P < .001$, respectively), while INTEM MCF, A10, and alpha angle significantly increased ($P < .001$) postoperatively, indicating that surgery further increases the coagulation potential.

Conclusion: A higher coagulation activity following hip fractures and surgical treatment can be detected by ROTEM shortly after the injury, even when this is undetectable by conventional coagulation assays.

KEYWORDS

hip fractures, hypercoagulability, rotational thromboelastometry, trauma-induced coagulopathy, viscoelastic method

1 | INTRODUCTION

Hip fractures are common injuries among elder population, the fastest growing part of the overall population, while their incidence is expected to further increase in the following years.[1,2] These injuries raise an important concern in public health because they are associated with a substantial financial cost due to their increased morbidity and mortality.[3] The recorded in-hospital and 1-year mortality for hip fractures are 12% and 22%, respectively.[4] The annual number of hip fractures in UK is 100 000 with an annual cost of about 2 billion pounds, while in the United States, the direct medical cost for every patient only for the 1st year is estimated at $40 000.[5,6] The high rate of complications such as venous thromboembolism (VTE) has also a significant impact on the socioeconomic implications of this hazardous medical entity; therefore, preventive measures and strategies for these complications are of great value.

In line with this, there is significant improvement in thromboprophylaxis following major orthopedic surgeries. Without thromboprophylaxis, the rates of pulmonary embolism (PE) and fatal PE following for hip fractures are 20%-27% and 0.6%- 7.5% respectively, and although use of anticoagulants has significantly decreased these numbers, the incidence of VTE, the second most common complication of these injuries, is still high.[7,8] Even though there are many contributing factors to the hypercoagulability seen in these patients, such as vessel wall injury, immobilization, and peritraumatic or perioperative blood loss, the exact pathophysiology of hypercoagulability is still unknown. A deeper knowledge of the hemostatic profile and of the alterations in the coagulation mechanism following hip fractures and subsequently following surgeries will aid in development of more effective preventive protocols.

Conventional laboratory assays of coagulation such as PT, INR, PTT fail to detect any changes in the coagulation profile of these patients, probably because these methods evaluate only a specific phase of coagulation. On the other hand, viscoelastic methods such as rotational thromboelastometry (ROTEM) have the advantage of an overall assessment of the clot formation and breakdown through a dynamic analysis of several aspects of coagulation. ROTEM analysis has the ability to detect various pathophysiological situations such as hypercoagulability or hyperfibrinolysis and to evaluate the coagulation profile of patients under LMWH therapy Therefore, ROTEM assay may be more suitable to detect a tendency toward hypercoagulability in these patients.

ROTEM parameters such as clotting time (CT), clot formation time (CFT), A10, alpha angle, and maximum clot firmness (MCF) can indicate a thrombotic state. CT corresponds to the induction of coagulation until the start of clot formation, while CFT corresponds to the subsequent period reflecting kinetics of thrombin formation.[9] Therefore, shorter clotting and clotting formation times indicate faster clot formation, thus hypercoagulability. MCF reflects stabilization of the clot and represents the consistency and quality of the clot, while the A10 parameter corresponds to the firmness of the clot.[9] Higher MCF and A10 values indicate a hypercoagulable state as well. Last, alpha angle describes the propagation phase of enzymatic factors that result in clot strengthening, with a higher value indicating a greater rate of clot strength growth, therefore a tendency toward hypercoagulability.[9-11]

The purpose of this study was to investigate changes in coagulation state following hip fractures by comparing ROTEM parameters in fractured patients and healthy adults. Furthermore, we aimed to evaluate similar changes in the hemostatic profile of these patients following surgical treatment by comparing preoperative and postoperative ROTEM parameters.

2 | METHODS

2.1 | Study design and subjects

The study cohort consisted of 198 patients with femoral neck and peritrochanteric fractures that were presented to the emergency department and admitted to the Orthopedic Department of the University Hospital "Attikon," over a 12-month period (7/2019 - 7/2020). All patients underwent surgery in the following days (usually the day after admission), including hip hemiarthroplasty or cephalomedullary nailing for femoral neck and peritrochanteric fractures, respectively. Patients received low molecular weight heparin (LMWH) postoperatively (4500 IU tinzaparin), starting 6-12 hours after surgery. A dose adjustment was performed for patients with renal impairment (for patients with eGFR <20 mL/min, the dose was adjusted accordingly; 2500 IU for patients 30-50 kg, 3500 IU for patients 50-150 kg, and 50 IU/kg for patients < 30 kg or > 150 kg). Tranexamic acid is not used in our hospital, while the transfusion protocol in our hospital indicates transfusion with RBC (red blood cells) units for patients with hemoglobin concentration lower than 8 g/dL, or if there are any signs of hemodynamic instability/anemia. Blood samples for analysis were collected and anticoagulated with 0.109 mol/L trisodium citrate (9:1, vol/vol blood anticoagulant) in parallel with routine blood draw at patient's admission and sent for ROTEM analysis. Similarly, a second ROTEM analysis was performed on a blood specimen that was collected on the 2nd postoperative day, again as part of the routine blood draws for hospitalized patients. The control group consisted of 52 healthy individuals that were matched for age and sex with the fractured patients. The control group was consisted of otherwise healthy adults who were screened preoperatively for minor orthopedic procedures. Patients and participants in the control group with coagulation disorders and those who were receiving oral anticoagulants were excluded from the study. Due to the high prevalence of antiplatelet agents in the population, patients on antiplatelet agents were not excluded in order to increase the clinical applicability of our results. An Institutional Review Board approval (ref. number: 501/19-07-2019) and a written consent from patients and healthy adults were obtained.

Data on demographics, past medical history, fracture type, surgical procedure, transfusion requirements, and conventional coagulation values including international normalized ratio (INR), prothrombin time (PT), activated partial thromboplastin time (PTT), and platelet count were recorded for each participant.

2.2 | Sample collection and ROTEM analysis

For the ROTEM analysis, a citrated tube was immediately filled with blood and analyzed in a ROTEM analyzer within 90 minutes from blood collection. It has been found that ROTEM results remain unaffected for blood samples stored at room temperature for up to 120 minutes after their collection.[12,13] Blood samples were analyzed in a ROTEM analyzer (ROTEM delta, Tem Innovations GmbH) as formerly described.[14] ROTEM analysis included EXTEM and INTEM assays preoperatively, and INTEM assays postoperatively. The following EXTEM and INTEM parameters were recorded: clotting time (CT, seconds), the time from the beginning of measurement until the formation of a clot 2 mm in amplitude; clot formation time (CFT, seconds), the time from CT (amplitude of 2 mm) until a clot firmness of 20 mm was achieved; amplitude recorded at 10 min (A10, mm); a angle (a°), the angle between the central line (x-axis) and the tangent of the TEM tracing at the amplitude point of 2 mm, describing the kinetics of clot formation; maximum clot firmness (MCF, mm), the final strength of the clot, and the lysis index at 60 min (LI60, %) which is the percentage of remaining clot stability in relation to the MCF following the 60-min observation period after CT which indicates the speed of fibrinolysis.

2.3 | Statistical analysis

We presented descriptive statistics of the study population for demographics, results of conventional coagulation assays, and ROTEM values. Data were presented as means ± standard deviations (SD), medians, and interquartile ranges (IQR), or percentages when appropriate. The 2 study groups, that is, healthy adults and patients with fractures were compared for these variables using the nonparametric Wilcoxon rank-sum test for noncategorical variables and the chi-square test for categorical variables. Additionally, the preoperative and postoperative ROTEM parameters for the group of patients with hip fractures were compared using the nonparametric Wilcoxon signed-rank test. Last, the independent impact of hip fracture trauma to the coagulation mechanism as evaluated by ROTEM values, adjusted for gender, age, smoking status, Charlson Comorbidity Index (CCI), and BMI was further assessed through linear regression analysis. The R software, version 3.6, was used for the statistical analysis. The Bonferroni correction to the nominal significance level was applied to address the issue of inflated type I error. Therefore, the critical level of significance for the comparison of ROTEM parameters between patients and healthy adults, as well as for the comparison of preoperative and postoperative ROTEM parameters, was set at 0.025 (=0.05/2) instead of 0.05. For all other tests, a *P*-value lower than .05 indicates statistical significance.

3 | RESULTS

In the first step, 281 participants (218 patients with femoral neck and peritrochanteric fractures that underwent surgery and 63 healthy adults) were screened as eligible for the study. Twenty-eight participants (17 patients and 11 healthy adults) were excluded from the study because they were receiving DOACs, vitamin K antagonists, or due to coagulation disorders. Moreover, 3 patients died before the postoperative blood draw for the postoperative ROTEM evaluation and they were also excluded from the analysis of our results. The final cohort consisted of 198 patients and 52 healthy adults. Patients with hip fractures had an average age of 78.9 ± 5.2 years, while the average age of healthy adults was 78.8 ± 4.3 years ($P = .95$). The BMI index was similar for the 2 groups (24.6 ± 3.6 and 23.8 ± 2.3 for fractured patients and healthy adults, respectively; $P = .33$), while the percentage of smokers was also similar for the 2 groups (7.5% for fractured patients and 9.6% for healthy adults; $P = .68$). 63.1% of the patients received blood transfusion with an average of 2.1 ± 0.7 RBC units, while none of the patients was transfused with any other blood products such as platelets or plasma. Moreover, none of the patients received coagulation factor concentrates or fibrinogen. The demographics and clinical parameters of the study population are summarized in Table 1.

TABLE 1 Characteristics of the study population

	Total (n = 250)	Patients with hip fractures (n = 198)	Control group (n = 52)	*P*-value
Age (years)	78.9 ± 5.1, 80 (76-82)	78.9 ± 5.2, 80 (76-82)	78.8 ± 4.3, 79 (77-83)	.95
Gender (males%)	109 (47.6)	93 (46.9)	16 (51.6)	.63
BMI (Kg/m^2)	24.5 ± 3.5,24 (22-27)	24.6 ± 3.6,24 (22-27)	23.8 ± 2.3,24 (22-25)	.33
Smoking	18 (7.6)	15 (7.5)	3 (9.6)	.68
CCI	5.6 ± 1.4, 6 (5-7)	5.9 ± 1.2, 6 (5-7)	3.4 ± 0.5, 3 (3-4)	**<.001**
Creatinine[a] (mg/dL)	1.16 ± 0.33, 1.07 (1.01-1.18)	1.18 ± 0.36, 1.09 (1.01-1.19)	1.08 ± 0.17, 1.04 (0.99-1.16)	.09
Antiplatelet medication	65 (26.0)	54 (27.2)	11 (21.1)	.37

Note: Data are presented as means ± SD, medians, and interquartile ranges (IQR), or as absolute values (percentages) when appropriate. The nonparametric Wilcoxon rank-sum test and the chi-square test were used for the comparison between the 2 groups. Significant difference at $p<0.05$ in bold

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index.

[a]Creatinine reference range: 0.8-1.3 mg/dL for male, 0.6-1.2 mg/dL for female.

TABLE 2 Conventional coagulation assays of the study cohort

Variables	Total (n = 250)	Patients with hip fractures (n = 198)	Control group (n = 52)	*P*-value
PLTs (count x10^3/ml)	216.2 ± 45.6, 211.0 (181.0-244.0)	218.9 ± 48.0, 216.0 (180.0-245.0)	203.8 ± 20.8, 201.0 (195.0-215.0)	.26
PTT (sec)	31.5 ± 3.8, 31.0 (29.0-34.0)	31.4 ± 3.9, 31.0 (29.0-34.0)	31.7 ± 2.7, 32.0 (29.7-34.0)	.41
PT (sec)	12.2 ± 2.0, 12.0 (11.0-14.0)	12.2 ± 2.0, 12.0 (11.0-14.0)	12.0 ± 1.6, 12.0 (10.8-13.2)	.50
INR ratio	1.06 ± 0.17, 1.04 (0.95-1.21)	1.06 ± 0.17, 1.04 (0.95-1.21)	1.05 ± 0.14, 1.04 (0.93-1.14)	.50

Note: Data are presented as means ± SD, medians and interquartile ranges (IQR). The nonparametric Wilcoxon rank-sum test was used for the comparison between the 2 groups.

Abbreviations: INR, international normalized ratio; PLTs, platelets; PT, prothrombin time; PTT, activated partial thromboplastin time.

3.1 | Analysis of preoperative data

The conventional coagulation parameters such as PT, PTT, INR, and platelet count did not significantly differ ($P < .05$) between the two study groups (Table 2). However, the comparison of preoperative ROTEM parameters between fractured patients and healthy individuals showed that patients with hip fractures had several significantly altered ROTEM parameters compared to healthy adults, indicating a higher coagulation potential following hip fractures (Table 3). Specifically, fractured patients had significantly higher EXTEM MCF ($P < .001$), EXTEM alpha angle ($P < .001$), INTEM MCF ($P < .001$; Table 3, Figure 1), INTEM A10 ($P < .001$), and INTEM alpha angle ($P < .001$), while they had significantly lower INTEM and EXTEM CT values ($P = .008$ and $P = .012$ respectively), and significantly lower INTEM and EXTEM CFT values ($P < .001$).

Moreover, multivariable regression analysis (adjusted for gender, age, smoking status, BMI, mortality, antiplatelet medication, and CCI index) showed that patients with hip fractures had significantly different EXTEM MCF ($P < .001$), CFT ($P < .001$), A10 ($P = .006$), and alpha angle ($P = .020$), and significantly different INTEM CT ($P = .021$), INTEM CFT ($P = .007$), INTEM MCF ($P < .001$), A10 ($P = .007$), and alpha angle ($P = .013$), further confirming the direct relationship between hip fractures and a higher coagulation potential (Table 4). The fact that EXTEM A10 was similar for both groups in the unadjusted comparison (Table 3) is probably due to a confounding factor, because EXTEM A10 was found to be significantly associated with presence of hip fracture in the multivariable regression analysis.

3.2 | Comparison of preoperative and postoperative data

Another interesting finding in our study was the impact of surgery on coagulation as evaluated by ROTEM parameters (Table 5). The postoperative INTEM CT value was lower than the preoperative INTEM CT value ($P = .008$), while also INTEM CFT significantly decreased postoperatively ($P < .001$). Moreover, the postoperative INTEM MCF, A10, and alpha angle were significantly higher than the respective preoperative values ($P < .001$ for all three parameters), indicating that surgery further induces coagulation activity.

4 | DISCUSSION

The findings of our study are in line with the existing body of evidence regarding the association of hypercoagulability with major trauma, fractures, and surgery.[4,15,16] Many EXTEM and INTEM parameters were significantly different between healthy adults and fractured patients indicating a faster clot formation, a higher absolute strength of the clot, and a greater rate of clot strength growth following hip fractures..[9]

To evaluate whether patients had a higher or lower coagulation activity postoperatively despite the use of LMWH, we performed INTEM analysis because there is some evidence although very limited that INTEM analysis can detect changes in coagulation activity due to LMWH.[17,18] There is only one clinical study that assessed the effect of prophylactic dose of LMWH on ROTEM parameters, which revealed that LMWH prolongs INTEM CT, although it was still within normal range.[18] Moreover, this effect of LMWH on INTEM CT was evident only on the 1st postoperative day and not on the 2nd postoperative day. Similarly, an in vitro study the authors found that INTEM CT was significantly prolonged by increasing concentrations of tinzaparin and enoxaparin, with significant correlation between LMWH dose and INTEM CT values.[19] However, as there are only limited data about the sensitivity of INTEM analysis to detect low levels of LMWH, there may be more appropriate methods to depict the effect of LMWH in ROTEM, such as the PiCT assay.[20] The pharmacokinetics of LMWH indicates that steady-state levels of LMWH are achieved after the 3rd dose of LMWH, which was usually given on the 1st postoperative day. Therefore, the ROTEM results that were obtained on the 2nd postoperative day reflected the established postoperative coagulation profile of these patients.[21] Interestingly, these patients showed a higher coagulation activity after surgery, despite the use of LMWH. This could indicate that the desirable thromboprophylactic protocol for a balanced coagulation profile that would effectively prevent VTE without a significantly increased risk for hemorrhage should be further investigated.

TABLE 3 EXTEM and INTEM parameters between the healthy adults and patients with hip fractures

Variables	Total (n = 250)	Patients with hip fractures (n = 198)	Control group (n = 52)	*P*-value*
EXTEM CT (sec)	60.6 ± 7.4, 60.0 (57.0-65.0)	59.8 ± 6.6, 60.0 (56.0-64.0)	63.7 ± 9.4, 61.5 (58.0-68.0)	**.012**
EXTEM CFT (sec)	85.6 ± 10.3, 85.0 (81.0-90.0)	84.0 ± 7.4, 84.5 (81.0-88.0)	91.7 ± 16.2, 91.5 (84.0-97.5)	**<.001**
EXTEM A10 (mm)	53.3 ± 4.6, 53.0 (50.0-57.0)	53.4 ± 4.6, 54.0 (51.0-57.0)	52.8 ± 4.9, 52.0 (49.0-57.0)	.24
EXTEM MCF (mm)	64.5 ± 6.8, 65.0 (61.0-68.0)	65.8 ± 5.6, 65.0 (63.0-69.0)	59.3 ± 8.6, 60.0 (58.0-63.5)	**<.001**
EXTEM Alpha angle (°)	73.2 ± 4.6, 73.0 (70.0-76.0)	73.7 ± 4.8, 74.0 (71.0-77.0)	71.3 ± 3.4, 71.5 (69.0-74.0)	**<.001**
EXTEM LI60 (%)	91.6 ± 5.2, 91.0 (88.0-95.0)	91.6 ± 5.4, 91.0 (88.0-95.0)	91.6 ± 4.4, 92.0 (89.0-95.0)	.74
INTEM CT (sec)	180.2 ± 7.1, 181.0 (177.0-184.0)	179.7 ± 7.3, 180.0 (176.0-184.0)	182.9 ± 4.9, 183.0 (180.0-186.0)	**.008**
INTEM CFT (sec)	69.3 ± 5.5, 70.0 (67.0-72.0)	68.9 ± 5.6, 69.0 (66.0-72.0)	71.9 ± 4.1, 72.0 (70.0-75.0)	**.001**
INTEM A10 (mm)	59.6 ± 6.0, 60.0 (56.0-63.0)	60.3 ± 6.0, 60.0 (57.0-64.0)	54.9 ± 4.2, 55.0 (51.0-58.0)	**<.001**
INTEM MCF (mm)	65.7 ± 5.5, 65.0 (63.0-69.0)	66.6 ± 5.2, 66.0 (64.0-69.0)	60.0 ± 3.6, 60.0 (59.0-62.0)	**<.001**
INTEM Alpha angle	78.7 ± 6.1, 78.0 (75.0-81.0)	79.3 ± 6.2, 79.0 (76.0-82.0)	75.0 ± 3.4, 75.0 (73.0-77.0)	**<.001**
INTEM LI60 (%)	89.7 ± 5.9, 90.0 (87.0-95.0)	89.8 ± 6.2, 90.0 (87.0-95.0)	89.0 ± 3.2, 89.0 (87.0-91.0)	.14

Note: Data are presented as means ± SD, medians, and interquartile ranges (IQR). The nonparametric Wilcoxon rank-sum test was used for the comparison between the 2 groups. Significant difference at $p<0.05$ in bold.

Abbreviations: A10, clot amplitude at 10 min; CFT, clot formation time; CT, clotting time; LI60, lysis index at 60 min; MCF, maximum clot firmness.

*The critical level of significance was set at .025.

Even though the complete pathophysiology of trauma-induced coagulopathy is not yet fully known, many aspects of this association between trauma and coagulopathy have been elucidated in recent years.[22] Cap and Hunt described three phases of trauma-induced coagulopathy following massive trauma.[23] The first phase is characterized by high thrombin generation, coagulation factor consumption, and increased fibrinolysis, reflecting consumption coagulopathy. The second phase takes place during resuscitation and is associated with therapy-related factors such as fluid resuscitation, while the third phase is evident in a later time and is associated with a prothrombotic state that predispose patients to venous thromboembolism. The fact that a hypercoagulable ROTEM pattern without any evidence of hyperfibrinolysis was found shortly after the injury and before prolonged bed rest in our study indicates that alterations in the hemostatic pathways possibly vary depending on the degree of the traumatic impact.

In patients with hip fracture undergoing surgery, trauma and endothelial damage are not the only factors resulting in hypercoagulability. Peritraumatic and perioperative blood loss, perioperative fluid resuscitation, and perioperative decreased mobility are also some of the other potential causes for hypercoagulability.[4] Ng and Lo reported that approximately 10% blood loss is linked with hypercoagulability.[24] Such blood loss is possible at the site of hip fracture during injury and later during surgery. The effect of hemodilution on coagulation is controversial.[25-27] Ogawa et al showed that dilution of whole blood led to delayed onset of thrombus formation and decreased thrombus growth, while Ruttman et al found that dilution of blood and plasma was linked with faster onset of coagulation.[25,27] Recent studies have also evaluated the effect of hemodilution with crystalloids or colloids on coagulation, based on viscoelastic assays.[28,29] Darlington et al found that 60% and 80% hemodilution with crystalloids or colloids significantly increased the clot formation time and decreased clot strength,[28] while Pathirana et al found that 40% hemodilution with colloids had a higher effect on coagulation, resulting in decreased coagulation activity, compared to hemodilution with crystalloids.[29] The patients in our study received isotonic crystalloids, specifically 9% NaCl solution for fluid replacement. Fluid administration was starting at their admission to the hospital, until adequate oral intake can be re-established, usually on the 1st postoperative day.

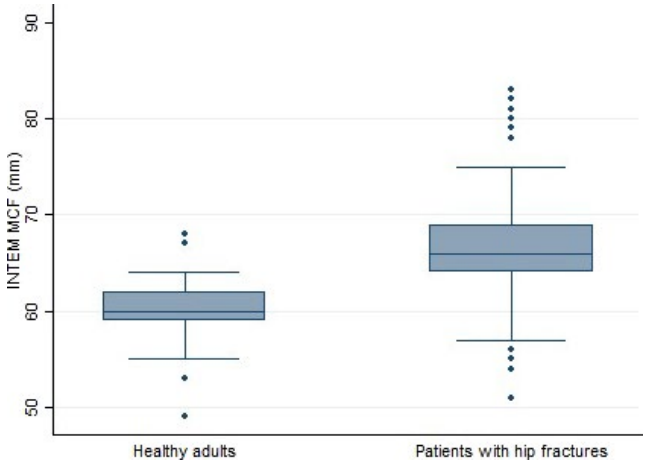

FIGURE 1 Boxplots of the preoperative INTEM MCF results of patients with hip fractures and INTEM MCF results of healthy adults [Colour figure can be viewed at wileyonlinelibrary.com]

Our results indicate that coagulation is induced immediately after the fracture which highlights the importance of early anticoagulant therapy for patients with hip fractures. The importance of early anticoagulant therapy is pointed out by Sorenson et al who demonstrated significant hemostatic activation as an immediate response to trauma following lower extremity fracture in a small group of patients who sustained femoral neck, femoral shaft, or tibial fracture.[30] Grant et al also highlighted that the risk for VTE following hip fracture starts at the time of injury rather than after surgery; therefore, they recommend immediate start of preventive anticoagulation.[31] Additionally, several scientific committees such as those of the National Institute for Health and Care Excellence (NICE) recommend initiation of LMWH at admission for patients with hip fractures.[32]

There are only 2 studies assessing the hemostatic profile of patients following hip fractures surgeries using viscoelastic methods. In both studies, the viscoelastic method was TEG and not ROTEM, while the study population in these studies was smaller compared to our study. These studies showed that these patients are in a hypercoagulable state and remain in this state following surgery despite the use of thromboprophylaxis, as was also seen in our study.[4,15] Wilson et al evaluated the effect of hip fracture surgery on whole blood coagulation in 250 patients.[4] The authors found that several TEG parameters differed significantly after the surgery, revealing a prothrombotic pattern. The TEG parameters that detected the hypercoagulable state in this study were k, MA, and alpha angle which reflect clot formation and clot strength. Interestingly, the respective ROTEM variables that assess the same aspects of coagulation were also significantly different in our study. In another study, Liu et al compared TEG values between 40 healthy individuals and 40 patients with hip fractures.[15] The authors found that several TEG parameters, including r, k MA, and alpha angle, were significantly different in fractured patients.

There are some limitations in our study that must be addressed. Even though the number of enrolled patients in our study is similar or higher than similar studies, larger studies are still required to validate the presented differences in ROTEM parameters. Also, power analysis to determine the sample size was not performed because as mentioned this is a pilot study using ROTEM parameters to detect changes in coagulation pattern after hip fractures. Moreover, we chose not to evaluate thromboembolic events in our study population; therefore, we did not compare ROTEM parameters between patients with and without VTE events. Given the reported incidence

TABLE 4 Results of multivariable regression analysis for the evaluation of the effect of hip fracture on ROTEM parameters adjusted for age, gender, BMI, CCI, antiplatelet medication, and smoking

	Presence of hip fracture		
Variables	Coefficient	95% CI	*P*-value
EXTEM CT (sec)	0.07	-1.41 - 0.56	.74
EXTEM CFT (sec)	-9.54	-13.03 - −6.06	**<.001**
EXTEM MCF (mm)	4.74	2.21 - 7.27	**<.001**
EXTEM A10 (mm)	3.07	0.87 - 5.27	**.006**
EXTEM alpha angle (°)	2.61	0.41 - 4.81	**.020**
INTEM CT (sec)	-4.00	-7.39 - −0.60	**.021**
INTEM CFT (sec)	-3.59	-6.19 - −0.99	**.007**
INTEM MCF (mm)	7.14	4.68 - 9.60	**<.001**
INTEM A10 (mm)	5.74	3.01 - 8.48	**.007**
INTEM alpha angle (°)	3.68	0.79 - 6.57	**.013**

Abbreviations: A10, clot amplitude at 10 min; CFT, clot formation time; CI, confidence interval, CT, clotting time; LI60, lysis index at 60 min; MCF, maximum clot firmness. Significant difference at $p<0.05$ in bold.

TABLE 5 INTEM parameters in patients with hip fractures before and after surgery

Variables	Preoperatively (n = 198)	Postoperatively (n = 198)	*P*-value*
INTEM CT (sec)	179.7 ± 7.3, 180.0 (176.0-184.0)	178.1 ± 8.3, 178.0 (174.0-182.0)	**.008**
INTEM CFT (sec)	68.9 ± 5.6, 69.0 (66.0-72.0)	56.4 ± 5.3, 58.0 (53.0-61.0)	**<.001**
INTEM A10 (mm)	60.3 ± 6.0, 60.0 (57.0-64.0)	62.2 ± 7.2, 63.0 (58.0-67.0)	**<.001**
INTEM MCF (mm)	66.6 ± 5.2, 66.0 (64.0-69.0)	72.8 ± 5.8, 72.5 (70.0-77.0)	**<.001**
INTEM Alpha angle	79.3 ± 6.2, 79.0 (76.0-82.0)	76.8 ± 4.6, 78.0 (73.0-80.0)	**<.001**
INTEM LI60 (%)	89.8 ± 6.2, 90.0 (87.0-95.0)	90.6 ± 3.9, 90.5 (88.0-93.0)	.45

Note: Data are presented as means ± SD, medians, and interquartile ranges (IQR). The nonparametric Wilcoxon signed-rank test was used for the comparison. Significant difference at $p<0.05$ in bold

Abbreviations: CT, clotting time; CFT, clot formation time; A10, clot amplitude at 10 min; MCF, maximum clot firmness; LI60, lysis index at 60 min.

*The critical level of significance was set at 0.025.

of these complications, the size of our population is not adequate to perform such comparisons between patients with and without VTE events. Last, studies for evaluation of the fibrinogen component of coagulation such as fibrinogen levels or FIBTEM assay, or other studies for detection of hypercoagulability such as TAT, F1/2 fragment were not performed.

Plasma-based routine coagulation assays cannot detect the higher coagulation activity that develops following hip fractures and surgical treatment, because trauma-induced coagulopathy is an evolving coagulopathy that involves whole blood elements and not only plasma coagulation factors. Therefore, ROTEM analysis may be a more suitable method, having also the advantage of detecting various other pathophysiological situations such as hyperfibrinolysis and the advantage of evaluating the coagulation profile of patients under LMWH therapy. Last, our results highlight the importance of immediate start of preventive anticoagulation treatment with LMWH or other anticoagulants at the time of admission, because patients with hip fractures have a higher coagulation activity shortly after the injury, rather than after surgical treatment.

CONFLICT OF INTEREST

The authors have nothing to declare.

AUTHOR CONTRIBUTIONS

AGT and AET conceptualized the project. AGT, DVP, SF, and AET designed the methodology. IGT, KAT, AFM, PK, ODS, VAA, DP, AGK, and PJP were involved in data collection, analysis, and interpretation. AGT wrote the manuscript. All the co-authors critically revised and finally approved the manuscript. All authors agree to be held accountable for all aspects of the work in insuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID


Andreas G. Tsantes https://orcid.org/0000-0002-3695-0759

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