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Clinical Article

Thromboelastometry-Based Prophylaxis for Venous Thromboembolism in the Acute Period Following Isolated Severe Traumatic Brain Injury

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ABSTRACT

Objective: Traumatic brain injury (TBI) is an independent risk factor for venous thromboembolism (VTE). This study aimed to determine the optimal timing for initiating pharmacological thromboprophylaxis for VTE in patients with isolated severe TBI using rotational thromboelastometry (ROTEM).
Methods: This single-center observational study enrolled 115 patients aged 18–59 years with isolated severe TBI within the first 48 hours after injury.
Results: Using ROTEM data, we identified hypercoagulation due to an increase in clot density (MCF EXTEM >72), which was attributed to fibrinogen (MCF FIBTEM >25). From day 4, hypercoagulation occurred in 14.8% of the patients. By day 7, these changes were observed in 85.2% of patients. According to brain computed tomography findings, patients who received early VTE chemoprophylaxis on days 3–4 after severe TBI did not experience progression of hemorrhagic foci.
Conclusion: Our results emphasize the clinical significance of thromboelastometry in patients with isolated severe traumatic TBI. Anticoagulant prophylaxis started on 3-4 days after severe TBI was relatively safe, and most patients did not experience hemorrhagic foci progression. The data acquired in this study may enable the optimization of VTE chemoprophylactic approaches, thereby reducing the associated risks to patients.

Keywords: Venous thromboembolism; Traumatic brain injury; Thrombelastography

INTRODUCTION

Traumatic brain injury (TBI) has long been recognized as an independent risk factor for the development of venous thromboembolism (VTE).[3,12,13] Previously identified independent predictors for VTE in TBI include age over 55 years, male sex, an Injury Severity Score of ≥15, lower-extremity injuries, and subarachnoid hemorrhage.[3] Moreover, the treatment for hypocoagulation in the acute period of TBI may contribute to an elevated risk of developing

Conflict of Interest
The authors have no financial conflicts of interest.

VTE.[5] However, most articles consider patients with TBI (both isolated TBI and general trauma with head injury) as a homogeneous group. In addition, guidelines on the optimal timing of pharmacological thromboprophylaxis initiation and data on its safety in patients with isolated TBI are lacking.

Numerous studies have reported that the risk of hemorrhage has historically led neurosurgeons to subjectively delay or avoid anticoagulation prophylaxis in patients with TBI.[11,12] A small retrospective study showed that only 42% of 88 patients with TBI received pharmacological thromboprophylaxis, and the mean time of anticoagulant initiation was 14 days.[2] Similarly, a multicenter retrospective study that investigated patients with TBI showed that pharmacological thromboprophylaxis was avoided in 25% of the patients for, at least, the first 7 days after TBI.[8] Thus, the initiation and timing of VTE chemoprophylaxis remain uncertain in this category of patients, entailing the implementation of more conservative and less effective methods in most patients, such as compression stockings and intermittent pneumatic compression.[12]

Conventional coagulation tests (CCTs), including the activated partial thromboplastin time (aPTT), prothrombin time (PT), and fibrinogen concentration, are often performed as screening tests; however, they do not reflect the general coagulation potential of patients. The advantage of viscoelastic hemostatic assays over CCTs is that they provide complete information regarding the density of blood clots formed (including the contribution of platelets and subsequent fibrinolysis), as well as characterize hemostatic properties in real time.

This study aimed to determine the optimal timing of pharmacological thromboprophylaxis initiation for VTE using rotational thromboelastometry (ROTEM). We hypothesized that viscoelastic hemostatic assays (such as ROTEM) could determine the ideal timing for safe initiation of pharmacological thromboprophylaxis for VTE in the acute period of isolated severe TBI.

MATERIALS AND METHODS

The current study enrolled patients (aged 18–59 years) with isolated severe TBI (Glasgow Coma Scale [GCS] score, ≤8 points; an Abbreviated Injury Scale [AIS] head score, ≤5 points in the presence of an AIS extracranial score, <1 point) who were hospitalized in the intensive care unit (ICU) within the first 48 hours of injury.

The exclusion criteria were as follows: massive blood loss due to bleeding, a history of coagulopathy, liver dysfunction, hypothermia (less than 35°C or therapeutic hypothermia), acidosis, prior neurosurgical intervention, coronary artery disease, prosthetic valves, previous anticoagulation therapy, use of any hemostatic agent (including fresh frozen plasma, cryoprecipitate, or tranexamic acid), kidney injury (acute or chronic), and pregnancy.

All patients were admitted to the intensive care unit and received recommended treatment during the acute period of TBI, including sedation and analgesia, invasive monitoring of hemodynamics, and intracranial pressure.[1,9]

Hemostatic assessment was performed on all patients immediately upon admission and every 24 hours thereafter. After the initiation of VTE chemoprophylaxis, samples were collected before anticoagulant injection.

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TABLE 1. Criteria of hemostasis state

Definition of hemostasis state	Criteria	
	CCT	ROTEM
Hypocoagulation	aPTT >35 sec, PT >13 sec, fibrinogen <1.7 g/L, or platelet count <150×10^9/L	CT INTEM >240 sec, CT EXTEM >79 sec, MCF INTEM <50 mm, MCF EXTEM <50 mm, and MCF FIBTEM <9 mm
Normal	aPTT 25–35 sec, PT 11%–13%, fibrinogen 1.7–4.4 g/L, and platelet count 150–410×10^9/L	CT INTEM 100–240 sec, CT EXTEM 38–79 sec, CFT INTEM 30–110 sec, CFT EXTEM 34–159 sec, A10 INTEM 44–66 mm, A10 EXTEM 43–65 mm, A10 FIBTEM 8–24 mm, MCF INTEM 50–72 mm, MCF EXTEM 50–72 mm, and MCF FIBTEM 9–25 mm
Hypercoagulation	N/A	ROTEM: CT INTEM <100 sec, CT EXTEM <38 sec, CFT INTEM <30 sec, CFT EXTEM <34 sec, A10 INTEM >66 mm, A10 EXTEM >65 mm, A10 FIBTEM >24 mm, MCF INTEM >72 mm, MCF EXTEM >72 mm, and MCF FIBTEM >25 mm

aPTT: activated partial thromboplastin time, PT: prothrombin time, CT: clotting time, INTEM: intrinsic coagulation assay, EXTEM: extrinsic coagulation assay, MCF: maximum clot firmness, FIBTEM: assay with recombinant tissue factor and cytochalasin D, CFT: clot formation time, N/A: not applicable.

The following CCTs were performed: aPTT, PT, Clauss fibrinogen assay (ACL TOP 300 CTS; Instrumentation Laboratory, Bedford, MA, USA), and platelet count assay (Sysmex XT 4000i; Sysmex Corporation, Kobe, Japan).

ROTEM (ROTEM Delta analyzer, Pentapharm GmbH, Munich, Germany) was performed concurrently with CCTs immediately after sample collection according to the standard protocol. This protocol included an intrinsic coagulation assay (INTEM) using kaolin, an extrinsic coagulation assay (EXTEM) with recombinant tissue factor, and an assay with recombinant tissue factor and cytochalasin D (FIBTEM), which permitted the evaluation of the isolated contribution of fibrinogen to clot firmness and completely eliminated the influence of platelets. The following variables were measured: clotting time (CT, s), clot formation time (CFT, s), maximum clot firmness (MCF, mm), and maximum lysis rate (ML, %). Because most ROTEM-based algorithms are based on four key variables (CT INTEM, CT EXTEM, MCF EXTEM, and MCF FIBTEM), we evaluated their implementation in pharmacological thromboprophylaxis initiation in patients with isolated TBI.

Based on the normal range, three conditions of hemostasis were diagnosed: hypocoagulation, normal coagulation, and hypercoagulation (**TABLE 1**).

All patients received mechanical methods of prophylaxis for VTE, including compression stockings starting the first 24 hours after admission to the ICU. We also analyzed VTE chemoprophylaxis in all participants, including the timing of its initiation. We assessed brain computed tomography scans after the initiation of VTE chemoprophylaxis. The outcomes were assessed according to the Glasgow Outcome Scale (GOS) at the time of the patient's discharge from the hospital.

Statistical assessment was performed using STATISTICA 6.0 (TIBCO Software Inc., Palo Alto, CA, USA). During statistical data processing, the normality of the distribution was determined using the Kolmogorov-Smirnov test. Data with normal distributions were presented as mean ± standard deviation. Median values (25th–75th percentiles) were used to present non-normally distributed data. The Mann–Whitney *U* test was performed to compare the outcomes of patients with or without VTE chemoprophylaxis. Differences were considered statistically significant at *p*-values of <0.05.

Ethics approval

This single-center observational study, which recruited patients with isolated TBI, was conducted in accordance with the principles of the Declaration of Helsinki, and close relatives of all individuals participating in the study provided written informed consent

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prior to enrollment. Study design was approved by local institutional ethics committee of Burdenko NeuroSurgery Center (No. 04/2018, 05.04.2018).

RESULTS

A total of 115 (91 males) patients (age, 31.8±10.7 years) in the acute period of severe isolated TBI were enrolled in the study after meeting the inclusion criteria.

CCTs revealed hypocoagulation in 57.4% of patients with severe TBI upon admission. The main indicators were an increase in PT (35%) and thrombocytopenia (17.4%), and 5% of patients had both thrombocytopenia and an increase in PT. ROTEM revealed signs of hypocoagulation in only 22.7% of the patients. None of the patients presented with hypercoagulation.

To analyze the dynamics of changes in hemostasis in patients with TBI, we assessed the CCTs and ROTEM data within 7 days after injury. The average aPTT values were within the normal range over the entire observation period - 30.2 [24.2, 36.1]. The mean PT values increased during the first 7 days - 16.45 s [13.5, 20.0]. No decrease in the fibrinogen levels was observed during the observation period. In contrast, an increase in the average fibrinogen values above the normal range of more than 4.4 g/L was observed for 5–6 days. Additionally, in the severe TBI group, thrombocytopenia persisted during the first 2 days at 134.0 platelets/L [116.5, 157.0], and normalization of this level was noted on the fifth day after TBI.

According to the ROTEM data (**TABLE 2**), hypocoagulable changes were observed in only 26.7% of the patients with severe TBI (GCS ≤8 points), and this was most often due to an increase in CT EXTEM for more than 79 s. The mean CT EXTEM was 73.0 s [61.0, 85.0]. A tendency toward normalization of this parameter was observed on days 2–3. Hypercoagulation, characterized by an increase in blood clot density, was observed in 14.8% of patients with severe TBI by day 4, which was characterized by an increase in blood clot density, MCF EXTEM 69.0 mm [62.5, 76.0], due to the contribution of fibrinogen. The MCF FIBTEM finding in these patients was 27.5 mm [19.0, 36.0]. These changes were characteristic of 85.2% of the patients with severe TBI by day 7.

We analyzed VTE chemoprophylaxis in all participants, including the timing of anticoagulant initiation. Enoxaparin sodium was used as an anticoagulant, and the dosage was based on anti-Xa activity peaks, with the target ranging from 0.2 to 0.5 units/mL.

In 101 patients, the decision to initiate VTE chemoprophylaxis was based on ROTEM data and was implemented on days 3–4 (3.75±1.7) after trauma in patients with severe TBI. In 14 patients, the decision to initiate VTE chemoprophylaxis was based on CCTs and was implemented after 7 days owing to prolonged PT and/or thrombocytopenia.

TABLE 2. Rotational thromboelastometry data within 7 days from the moment of injury

Variables	Day after TBI						
	1	2	3	4	5	6	7
INTEM CT (sec)	219.0 [170.0, 244.0]	186.5 [151.0, 281.0]	188.0 [144.0, 207.0]	189.5 [147.0, 204.0]	176.5 [144.0, 192.0]	166.5 [123.0, 180.0]	150.5 [102.0, 169.0]
EXTEM CT (sec)	73.0 [61.0, 85.0]	61.0 [54.5, 63.5]	59.0 [59.0, 67.0]	66.0 [56.0, 71.5]	65.0 [56.5, 70.0]	63.0 [56.5, 72.0]	53.0 [50.5, 62.0]
EXTEM MCF (mm)	54.0 [52.0, 60.0]	56.0 [58.0, 63.0]	60.0 [59.0, 66.0]	68.0 [59.5, 74.0]	69.0 [62.5, 76.0]	74.0 [64.0, 77.0]	76.0 [69.0, 81.0]
FIBTEM MCF (mm)	17.0 [12.0, 19.5]	19.0 [13.5, 20.0]	20.0 [15.5, 22.5]	23.0 [18.5, 27.5]	27.5 [19.0, 36.0]	29.5 [21.0, 38.0]	35.0 [23.0, 41.0]

TBI: traumatic brain injury, INTEM: intrinsic coagulation assay, CT: clotting time, EXTEM: extrinsic coagulation assay, MCF: maximum clot firmness, FIBTEM: assay with recombinant tissue factor and cytochalasin D.

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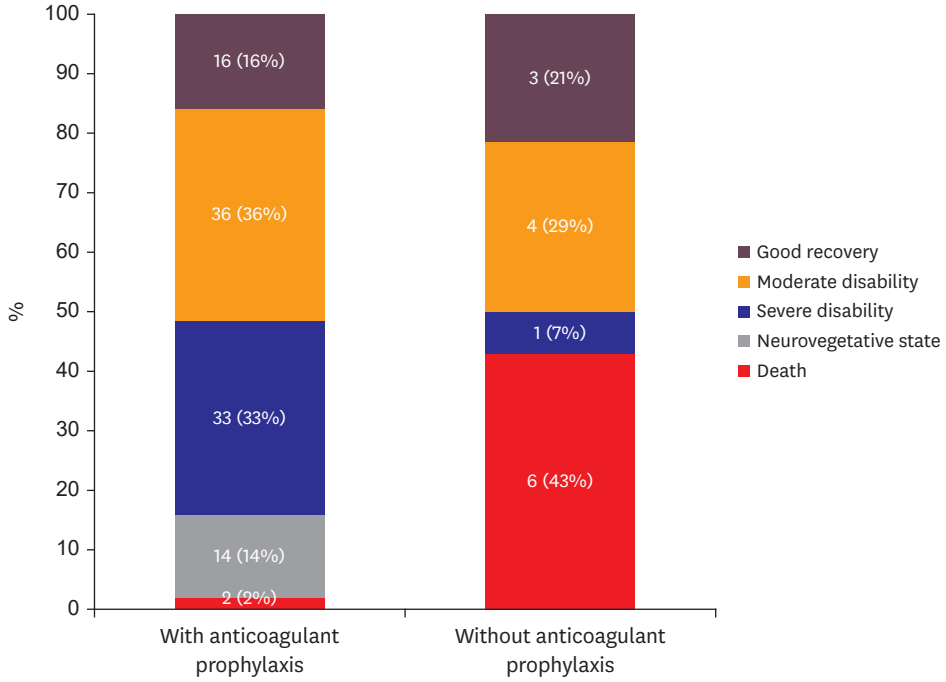

FIGURE 1. Comparison of Glasgow Outcome Scale in patients with or without venous thromboembolism chemoprophylaxis based on rotational thromboelastometry.
Values are presented number (%).
Fisher exact test, *p*-value <0.001 (n=115).

A comparison of GOS scores in patients with or without VTE chemoprophylaxis based on ROTEM is presented in **FIGURE 1**. Participants with early VTE chemoprophylaxis did not exhibit progression of hemorrhagic foci according to brain computed tomography findings.

DISCUSSION

Excessive anticoagulation, which might lead to hemorrhagic manifestations, as well as refusal of VTE chemoprophylaxis, resulting in pulmonary embolism, is associated with a clear risk of poor outcomes in patients with TBI. Several studies[4,11] have suggested that thorough consideration of all risk factors can contribute to the rational stratification of patients with TBI into high- and low-risk groups for VTE, which can form the basis of an individualized therapeutic approach.

Most studies[2-5,12,13] have used a repetitive approach while considering the optimal time for initiating VTE chemoprophylaxis, as patients with TBI have historically been considered a homogeneous group. However, the acute period of TBI includes a spectrum of conditions that can include patients with a small traumatic subarachnoid hemorrhage and a relatively high level of consciousness, as well as patients with severe diffuse axonal injury, diffuse edema, and intracranial hypertension, who require multimodal monitoring. Therefore, a unified approach for initiating VTE chemoprophylaxis in patients with severe or mild TBI is not justified. The data from the current study indicate the state of hemostasis in patients with severe TBI.

One of the most significant advantages of thromboelastometry is its ability to detect hypercoagulation. Hypercoagulation was identified using ROTEM, which often

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remains undiagnosed using conventional CCTs. Starting on day 4, hypercoagulation appeared in 14.8% of patients with severe TBI due to an increase in clot density. By day 7, hypercoagulation was observed in 85.2% of the patients with severe TBI.

Massaro et al.[6] identified a delayed hypercoagulable state after TBI using thromboelastography, which was explained by platelet hyperactivity after trauma, with an elevated maximum amplitude representing increased clot strength. Midura et al.[7] also focused on the phenomenon of hypercoagulation after TBI. They assessed the activity of platelets and microvesicles in a murine model of moderate TBI using ROTEM and platelet counts, in addition to nanoparticle tracking assessment and functional analysis. They reported an increase in MCF EXTEM and MCF FIBTEM 24 hours after TBI. As mentioned above, FIBTEM is an assay that uses recombinant tissue factor and cytochalasin D, which permits the evaluation of the isolated contribution of fibrinogen to clot firmness, completely eliminating the influence of platelets. The data also showed that the total density of the blood clots remained unchanged despite a decrease in platelet contribution.

Based on the ROTEM data, VTE chemoprophylaxis in our study was initiated 3–4 days after severe TBI. This anticoagulant prophylactic approach was relatively safe; most patients did not experience hemorrhagic foci progression according to brain computed tomography findings or any other clinical signs of hemorrhage.

Leaving a 72 hours window without VTE chemoprophylaxis is necessary for all patients with isolated severe TBI. The primary reason for this is the possible requirement for invasive interventions, such as intracerebral pressure monitoring, tracheostomy, and in some cases, decompressive craniotomy. Second, the signs of hypocoagulation, the detection of which is possible upon admission of the patient, regress within 3–4 days according to our data, making the initiation of VTE chemoprophylaxis safe.

Factors that can prevent pharmacological thromboprophylaxis include the use of anticoagulants or antiplatelet therapy before hospitalization, known coagulopathies, active bleeding, and the absence of normal homeostatic parameters. In such cases, the timing of initiating VTE chemoprophylaxis should be based on the clinical data of each patient. Enoxaparin sodium was used as the optimal anticoagulant, similar to most studies on VTE chemoprophylaxis.[10]

Limitations of the study

The approach described here can only be applied to patients who meet the inclusion and exclusion criteria. Patients with coagulopathies due to drug effects or liver diseases were excluded. The patients with TBI in this study met the AIS head ≤5 points and AIS extracranial <1 point criteria; therefore, no active extracranial bleeding was present that might have affected hemostasis. Implementation of VTE chemoprophylaxis in patients with coagulopathy or active extracranial bleeding requires further research.

CONCLUSIONS

Our results emphasize the clinical significance of thromboelastometry in patients with isolated severe TBI. Anticoagulant prophylaxis started 3–4 days after severe TBI was relatively safe. Most patients did not experience hemorrhagic foci progression according to brain computed tomography findings or any other clinical signs of hemorrhage. The data acquired

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in this study may enable the optimization of VTE chemoprophylactic approaches, thereby reducing the associated risks to patients.

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