Correlations between rotational thromboelastometry (ROTEM) and standard coagulation tests following viper snakebites

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Abstract

Background: A high prevalence of venom-induced consumption coagulopathy has been reported in individuals with viper snakebites. Rotational thromboelastometry (ROTEM) is a rapid technique that could be advantageous in assessing and monitoring coagulation disorders.
Purpose: To explore correlations between ROTEM and standard coagulation tests.
Patients and methods: This prospective observational study was performed among 41 patients with viper envenomation admitted to the Vietnam Poison Control Center from April 2016 to October 2017. Standard coagulation measurements [platelet count, prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen level] and ROTEM indicators [clotting time (CT), amplitude (at set time: 5 and 10 minutes), clot information time (CFT) and maximum clot firmness (MCF) for extrinsic (EXTEM), intrinsic (INTEM), and fibrin based (FIBTEM) ROTEM] were obtained.
Results: For INTEM, EXTEM, the FIBTEM, proportions of patients with prolonged CT were 34.1%, 63.4%, and 61.0% respectively and the proportions of patients with decreased MCF were 62.2%, 62.2%, and 35.5%, respectively. Moderate correlations were observed between PT and

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EXTEM CT (r = 0.627), aPTT and INTEM CT (r = 0.626), fibrinogen and FIBTEM MCF (r = 0.723), and platelet count and EXTEM MCF (0.60).
Conclusion: ROTEM indicated a hypocoagulation state in patients with viper snakebite and was moderately correlated with standard coagulation parameters.

Introduction

Venomous snake bites are life-threatening conditions, especially in tropical countries where individuals live in close proximity to venomous snakes and treatment delays are associated with limited access to medical care.[1–4] The complex toxins present in snake venom may affect any part of the body and cause diverse clinical complications resulting from coagulopathic, neuropathic, myotoxic, and necrotic effects.[2,5–7] Coagulopathy resulting from poisonous snake bites is a common and dangerous condition. In Vietnam, the Viperidae are one of the principal terrestrial venomous snake families.[8] The coagulopathic effects of viper venom result from consumption or inhibition of coagulation factors resulting in widespread bleeding, also known as venom-induced consumption coagulopathy.[7,9,10] The patient falls into a state of disseminated intravascular coagulation wherein soluble fibrin is produced, causing the appearance of small blood clots scattered in the lumen. The process of fibrinolysis leads to excessive consumption of coagulation factors, tissue ischemia, tissue hypoxia, and bleeding.[9,11,12]

Rotation thromboelastometry (ROTEM) is increasingly used as a tool to assess and monitor coagulation disorders. This method measures viscoelastic changes that occur during blood clot formation, providing a graphical representation to describe the interactions between components such as clotting factors and inhibitors, fibrinogen, thrombocytes, and the fibrinolysis system.[13] ROTEM has been shown to have a faster turnaround time than standard laboratory tests. Initial results can be provided within 5 to 10 minutes, much faster than standard coagulation measurements such as prothrombin time (PT), activated partial thromboplastin time (aPTT), platelet count, international normalized ratio (INR), and fibrinogen level (these generally require 30 to 90 minutes). Furthermore, ROTEM is easy to use in an emergency context and is capable of detecting and quantifying comprehensive hemostatic conditions such as thrombocytopenia, factor deficiency, heparin effect, hypofibrinogenemia, and hyperfibrinolysis.[13,14] ROTEM has been used to predict blood loss and as a guide to blood product and drug administration in patients undergoing cardiac and hepatic surgery.[9] A previous study of trauma patients showed that use of ROTEM clotting time (CT) instead of PT/aPTT to assess coagulation disorders produced better results.[15]

Previous studies comparing ROTEM standard laboratory tests have primarily focused on patients with trauma or patients undergoing major surgery.[13] Few studies have assessed the use of ROTEM for evaluation of coagulopathy and its correlations with standard coagulation parameters,

especially in patients with viper snakebites. Understanding the clotting process and coagulation defects early during hospital admission by applying functional coagulation tests such as ROTEM may significantly improve the effectiveness of treatments and patient prognosis. Therefore, the aim of this study was to explore correlations between the results of ROTEM and standard coagulation tests (PT, aPTT, fibrinogen level, and platelet count) in patients with viper snakebites in Vietnam.

Materials and methods

This prospective observational study was performed among all viper snakebite patients who presented at the Poison Control Center at Bach Mai Hospital, Vietnam from November 2016 to October 2017. The study was approved by the Ethics Committee of Bach Mai Hospital (reference number: 3377/QD-BM). Written informed consent was obtained from all patients or their guardians.

Patients were included if they had a confirmed history of viper snakebite and developed features of envenomation. The viper snake bite was determined when patients met criterion 4 and at least one of criteria 1, 2, or 3: (1) presence of fang marks; (2) presence of swelling, ecchymosis, cellulitis, necrosis, blister formation, and/or bleeding from local sites; (3) disturbances in coagulation mechanisms with or without systemic bleeding; and (4) identification of the snake responsible for the bite by the patient or others (e.g., presentation of the dead snake in the hospital or identification of the snake from an image). Dead snakes and photographs were sent to identification specialists at the Museum of Nature, Vietnam Academy of Science and Technology. The specimens were confirmed to belong to the Viperidae family.

Patients were excluded from the study if they met any of the following criteria: (1) lack of signs or symptoms of envenomation after a period of observation; (2) history of pre-existing renal disease, liver dysfunction and/or bleeding disorder; (3) history of use of blood products, anticoagulants, or other specific therapies prior to hospital admission (e.g., steroids or immunoglobulin); and (4) refusal to participate in the study.

Measures and instruments

Data were collected using a structured questionnaire that assessed the following parameters: general characteristics (age and sex), place of snake bite (home, garden, mountain, or other), viper snake type (*Trimeresurus albolabris*, *T. mucrosquamatus*, *T. cornutus*, *Deinaglistrodon acutus,* or undefined), time between bite and hospitalization (hours), bleeding events (bleeding at site of snakebite, skin hemorrhage, gastrointestinal hemorrhage, muscle bleeding, gum bleeding), duration of hospitalization (days), and outcome (death or survival).

Blood tests

Blood samples were obtained at the time of admission, including two samples of citrated and one sample of ethylenediaminetetraacetic acid (EDTA)-treated whole blood. Platelet counts were determined in the EDTA-treated sample. PT (% activity, PT %), aPTT, and fibrinogen level (g/L) were determined using one of the two citrated blood samples for each patient. PT, aPTT and fibrinogen level were determined using the ACL TOP 500 CTS (Instrumentation Laboratory, Bedford, MA, USA). Platelet counts were analyzed using the CELL-DYN Sapphire Hematology Analyzer (Abbott, Chicago, IL, USA).

ROTEM

The second citrated whole blood sample was used for rotational ROTEM at the

time of admission using the ROTEM® delta system (TEM Innovations GmbH, Munich, Germany). ROTEM analyses were performed directly after blood was drawn.

Three ROTEM variables were evaluated in the context of this study: (1) extrinsic ROTEM (EXTEM); (2) intrinsic ROTEM (INTEM); and (3) fibrin-based ROTEM (FIBTEM).[16] EXTEM measures contact activation and provides information about the extrinsic coagulation pathway, similar to aPTT. INTEM measures tissue factor activation and provides information about the intrinsic coagulation pathway, similar to PT. FIBTEM uses cytochalasin D, an actin polymerization inhibitor, to block the platelet contribution to clot formation, leaving only the impact of fibrin formation and polymerization to be measured.

ROTEM tests were performed to analyze the following parameters: clotting time (CT), amplitude (at set times: 5 and 10 minutes), clot information time (CFT), and maximum clot firmness (MCF) for each of EXTEM, INTEM, and FIBTEM. In addition, maximum lysis (ML) was assessed only for EXTEM and FIBTEM. CT was defined as the time (in seconds) from the start of the test until an amplitude of 2 mm was reached. CFT was defined as the time required for clot amplitude to increase from 2 to 20 mm. MCF is the maximum amplitude (in mm) of the clot. A5 and A10 represent clot firmness (in mm) after 5 and 10 minutes of the test. ML was defined as the maximum degree of lysis of the blood clot. Technical details of ROTEM have been published elsewhere.[13]

Data analysis

This was a sample of convenience during the study period. The SPSS software package version 22.0 (IBM Corp., Armonk, NY, USA) was used for statistical analyses. Continuous variables were presented as means $+/-$ standard deviations (SDs) and medians with interquartile ranges. Categorical variables were summarized as frequencies and percentages.

Spearman's correlation was used to measures the strength and direction of monotonic associations between the following variables: EXTEM CT with PT, EXTEM MCF with platelet count, INTEM CT with aPTT, and FIBTEM MCF with fibrinogen level.

Results

The study enrolled 45 patients from November 2016 to October 2017. After assessing inclusion/exclusion criteria and obtaining informed consent, 41 participants met the eligibility criteria and agreed to participate in this study.

Table 1 shows the general characteristics of the study population. Participants had a mean (SD) age of 41.3 (14.7) years. The majority (63.4%) of patients were bitten in the mountains. The most common snake responsible for bites was *T. albolabris* (53.7%). The mean (SD) time between bite and hospital admission was 21.32 (18.85) hours (Table 1).

The proportion of patients with ML >15% was highest for EXTEM (51.4%). Using FIBTEM, the prevalence of ML <10% was 58.0% (Table 2).

Table 3 shows the characteristics of ROTEM (A5, A10, MCF, and CT derived from INTEM, EXTEM, and FIBTEM).

Figure 1 shows correlations between the following variables: (1) EXTEM CT and PT % on admission (Figure 1a), (2) INTEM CT and APTT on admission (Figure 1b), (3) FIBTEM MCF and fibrinogen level on admission (Figure 1c), and (4) EXTEM MCF and platelet count on admission (Figure 1d). EXTEM CT and PT % on admission (Figure 1a) were moderately negatively correlated (p < 0.001). The scatterplot between APTT % and INTEM CT on admission (Figure 1b)

Table 1. General characteristics of study participants.

Characteristics	N = 41 (%)
Sex	
Female	16 (39)
Male	25 (61)
Place of snake bite	
Home	5 (12.2)
Garden	8 (19.5)
Mountain	26 (63.4)
Other	2 (4.9)
Duration of hospitalization (days)	
1–5	24 (58.5)
6–10	15 (36.6)
>10	2 (4.9)
Snake type	
Trimeresurus albolabris	22 (53.7)
Trimeresurus mucrosquamatus	7 (17.1)
Trimeresurus cornutus	1 (2.4)
Deinaglistrodon acutus	1 (2.4)
Undefined	10 (24.4)
Death	0 (0.0)
Standard coagulation of patients	
Platelet decreased	14 (34.1)
PT % decreased	16 (39.0)
aPTT prolonged	7 (17.1)
INR increased	29 (70.7)
Bleeding events	
Bleeding at snake bite place	15 (36.6)
Skin hemorrhage	26 (63.4)
Gastrointestinal hemorrhage	3 (7.3)
Muscle bleed	29 (70.7)
Gums bleeding	2 (4.9)
	Mean (SD)
Time delay to hospital admission (hours)	21.32 (18.85)
Age (years)	41.3 (14.7)
PT on admission	70.4 (32.8)
aPTT on admission	41.2 (29.8)
Fibrinogen levels on admission	1.6 (1.2)
Platelet count on admission	164.0 (108.3)
CT INTEM on admission	589.2 (1108.6)
CT FIBTEM on admission	1270.8 (2004.6)
CT EXTEM on admission	496.6 (1138.0)
CFT INTEM on admission	335.9 (518.5)
CFT FIBTEM on admission	634.7 (232.3)
CFT EXTEM on admission	289.6 (355.6)
MCF INTEM on admission	43.8 (16.0)

(continued)

Table 1. Continued.

Characteristics	N = 41 (%)
MCF FIBTEM on admission	11.2 (6.9)
MCF EXTEM on admission	42.3 (17.9)
DIC score	3.4 (2.7)
	Range
Delay in presentation to hospital (hours)	2–81

PT, prothrombin time; aPTT, activated partial thromboplastin time; INR, international normalized ratio; SD, standard deviation; CT, clotting time; INTEM, intrinsic rotational thromboelastometry; EXTEM, extrinsic rotational thromboelastometry; FIBTEM, fibrin-based rotational thromboelastometry; CFT, clot information time; MCF, maximum clot firmness; DIC, disseminated intravascular coagulation.

Table 2. Characteristics of EXTEM and FIBTEM maximum lysis.

ML (%)	EXTEM, N (%)
<5	4 (10.8)
5 ≤ ML ≤15	14 (37.8)
>15	19 (51.4)
	FIBTEM, N (%)
<10	18 (58.0)
≥10	13 (42.0)

Note: data for ML by EXTEM were missing for four patients, while data for ML by FIBTEM were missing for 10 patients.
EXTEM, extrinsic rotational thromboelastometry; FIBTEM, fibrin-based rotational thromboelastometry; ML, maximum lysis.

showed a moderate positive correlation (p < 0.001). Figure 1c and Figure 1d show moderate positive correlations between MCF EXTEM on admission and fibrinogen (Figure 1c) and between MCF EXTEM on admission and platelet count (Figure 1d) (both p < 0.001).

Discussion

In this study, ROTEM was used to identify hypocoagulation status associated with

Table 3. ROTEM parameters measured in this study.

	A5		A10		MCF		CT (s)		CFT	
	Median (IQR)	N (%)	Median (IQR)	N (%)	Median (IQR)	N (%)	Median (IQR)	N (%)	Median (IQR)	N (%)
INTEM										
Decreased	28 (17.5, 39.5)	32 (86.5)	38 (26.5, 49.5)	25 (67.5)	48 (36.5, 56)	23 (62.2)	213 (177.5, 358)	0 (0)	165 (92, 276.5)	8 (19.5)
Normal		5 (13.5)		12 (32.4)		14 (37.8)		27 (65.9)		0 (0)
Increased		0 (0)		0 (0)		0 (0)		14 (34.1)		33 (80.5)
Total		37 (100)		37 (100)		37 (100)		41 (100)		41 (100)
		(missing: 4)		(missing: 4)		(missing: 4)				
EXTEM										
Decreased	28 (16.5, 38.5)	24 (64.9)	38 (26, 48.5)	24 (64.9)	48 (29.5, 57.5)	23 (62.2)	91 (62, 267.5)	0 (0)	165.5 (99, 341.8)	9 (22)
Normal		13 (35.1)		13 (35.1)		14 (37.8)		15 (36.6)		0 (0)
Increased		0 (0)		0 (0)		0 (0)		26 (63.4)		32 (78)
Total		37 (100)		37 (100)		37 (100)		41 (100)		41 (100)
		(missing: 4)		(missing: 4)		(missing: 4)				
FIBTEM										
Decreased	9 (4, 12)	13 (41.9)	10 (4, 13)	9 (29)	12 (4, 14)	11 (35.5)	87 (57.5, 2407)	0 (0)	680 (383, –)	38 (92.7)
Normal		18 (57.1)		21 (67.7)		19 (61.3)		16 (39)		0 (0)
Increased		0 (0.0)		1 (3.2)		1 (3.2)		25 (61)		3 (7.3)
Total		31 (100)		31 (100)		31 (100)		41 (100)		41 (100)
		(missing: 10)		(missing: 10)		(missing: 10)				

ROTEM, rotational thromboelastometry; A5, clot firmness (in mm) after 5 minutes; A10, clot firmness (in mm) after 10 minutes; MCF, maximum clot firmness; CT, clotting time; CFT, clot information time; IQR, interquartile range; INTEM, intrinsic rotational thromboelastometry; EXTEM, extrinsic rotational thromboelastometry; FIBTEM, fibrin-based rotational thromboelastometry.
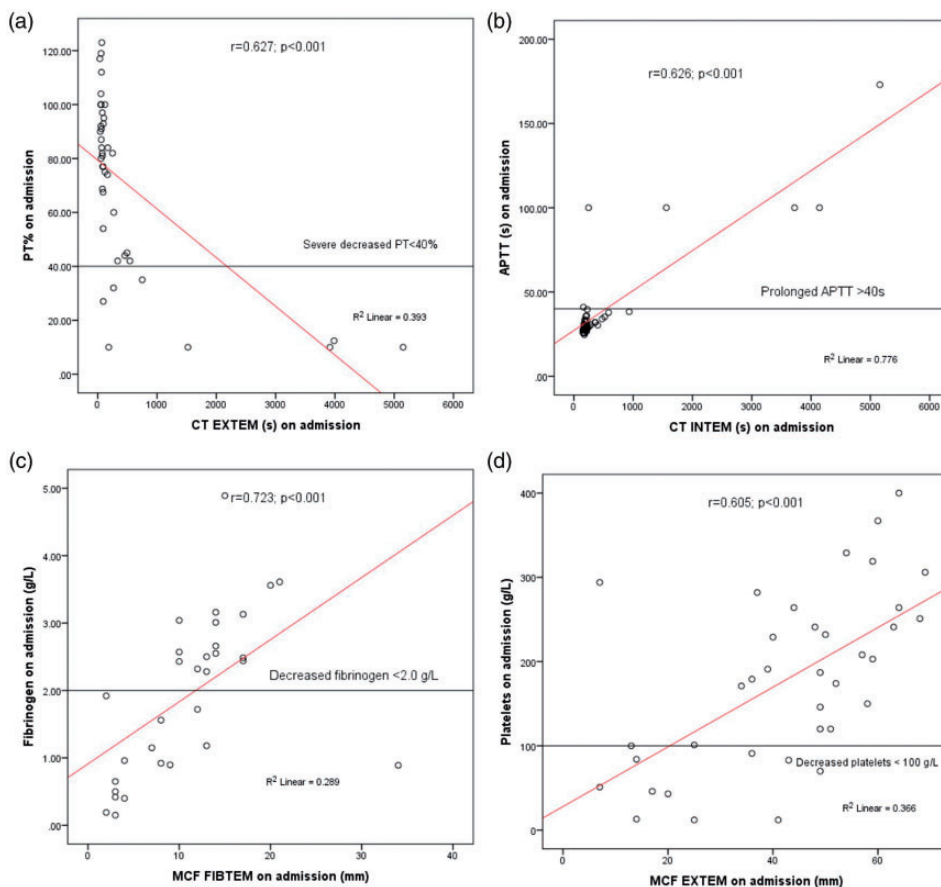
Figure 1. Correlations between ROTEM parameters and standard coagulation tests (PT %, aPTT %, fibrinogen, and platelet counts). Correlations between (a) EXTEM CT and PT % on admission, (b) INTEM CT and aPTT on admission, (c) FIBTEM MCF and fibrinogen level on admission, and (d) EXTEM MCF and platelet count on admission.
PT, prothrombin time; aPTT, activated partial thromboplastin time; CT, clotting time; EXTEM, extrinsic rotational thromboelastometry; INTEM, intrinsic rotational thromboelastometry; FIBTEM, fibrin-based rotational thromboelastometry; MCF, maximum clot firmness; ROTEM, rotational thromboelastometry.

deficiencies of clotting factors and fibrinogen (CT prolonged, MCF decreased) among viper snakebite victims in Vietnam. Our findings support those of other studies addressing coagulopathy after snakebites using ROTEM.[17–19] Additionally, we found moderate correlations between ROTEM parameters and the results of standard coagulation tests and platelet counts.

Deficiency of clotting factors and fibrinogen is a well-described mechanism of snakebite-associated coagulopathy.[9] The venoms of viper snakes contain various pro-coagulant toxins.[12] When the human hemostatic system is exposed to these toxins, the clotting cascade is activated. As clotting factors are depleted, little or no clotting factors remain in circulation. The primary elements of venom that affect

fibrinolysis are plasminogen activators and fibrinolytic enzymes. Fibrinogen clotting and fibrinolytic snake venom toxins directly affect thrombus-forming proteins. Fibrinogen may be split into fibrin and then into degradation products, or may be only partially split, yielding an ineffective form of circulating fibrinogen. The end result of either mechanism is a tendency toward increased bleeding.[12] Venoms containing plasminogen-activating toxins also enhance fibrinogen deficiency.

In accordance with the results of other studies, our data indicated significant correlations between: (i) PT or aPTT and the CTs from EXTEM and INBTEM: (ii) fibrinogen levels and the MCF from FIBTEM; and (iii) platelet counts and the MCF from EXTEM [20,21]. Both plasma-based coagulation tests and ROTEM CT evaluate the activity of soluble coagulation factors. Typical coagulometric measurements (e.g., PT and aPTT) measure only the clotting time corresponding to the initiation phase of the coagulation process and the endpoints of these tests occur after the formation of only 5% of total thrombin [22]. Consequently, aPTT and PT reflect only the initial coagulation process while the formation of thrombin and fibrin is still ongoing. In contrast, EXTEM and INTEM CT capture the time from activation of the extrinsic pathway by tissue factor or ellagic acid to the start of clot building in a whole-blood sample and evaluate the initiation phase of thrombin generation.

A positive correlation between MCF and fibrinogen has previously been reported; both methods assess fibrinogen cleavage to fibrin.[21,23] However, they differ in terms of the examined sample, activator, end point determination, and output.[24–26] Rotational thromboelastometry has the advantage of revealing distinct patterns suggestive of generalized clotting factor deficiency or isolated fibrinogen deficiency; basic coagulation tests do not distinguish between these situations. Fibrin strength can be measured and represented as the MCF or maximal amplitude values in ROTEM tests. Although fibrinogen concentration is the main determinant of FIBTEM MCF, this parameter also depends on the availability of factor XIII and the coagulation factors of the extrinsic pathway, including erythrocytes and functional fibrinogen. Therefore, FIBTEM MCF evaluates the additional effects of blood cellular components on clot strength. Importantly, FIBTEM visualizes clots that form from cross-linked fibrin strands, erythrocytes, and factor XIII and provides additional information regarding clot strength and clot lysis. The FIBTEM MCF is believed to predict the function of fibrinogen and is increasingly used to provide guidance regarding fibrinogen treatment.[27,28] Furthermore, ROTEM offers faster turnaround times, which could be beneficial for timely monitoring and determining the course of coagulation therapy.

Although ROTEM is a valuable addition to the set of diagnostic tools used for coagulation management, is currently mainly used at tertiary care hospitals, while the technology for measuring PT/INR and PTT is more widely available. Even though these methods use whole blood, they are still artificial systems that completely ignore flow dynamics; therefore, they cannot detect disorders of primary hemostasis or be used to diagnose von Willebrand's syndrome.[29]

Our study has several implications. Our data provide some of the first insights regarding coagulopathy after viper snakebites in Vietnam. In our study, coagulation was comprehensively evaluated through coagulation tests and ROTEM. The study also had several limitations. First, this study investigated patients at a tertiary hospital. Thus, the patients included in this study may have experienced more severe snakebites than individuals treated in local

hospitals or in community settings. Study data were obtained at a single time point, so the reliability of our findings over time is unclear. The sample size was relatively small, and subsequent studies of larger number of patients will be necessary to support and confirm our findings. Although several causes of coagulopathy were excluded, data for some factors associated with coagulopathy (e.g., patient weight and comorbidities) were not assessed. Finally, we did not record ROTEM or standard coagulation test times, limiting the precision for estimating the time-based advantages of ROTEM over standard coagulation tests.

Conclusion

Results obtained using ROTEM indicated a hypocoagulation status in viper snakebite patients in Vietnam. We observed moderate correlations between standard coagulation parameters and platelet counts. ROTEM also revealed distinct patterns suggestive of generalized clotting factor deficiency or isolated fibrinogen deficiency that was not detected by standard clotting tests.

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