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Topical Update: Viscoelastic Haemostatic Assays in Clinical Practice

Authors: Dr Joyce KWONG and Dr Eudora CHOW, Consultant Haematologists, Department of Pathology, United Christian Hospital, Hospital Authority

Editorial Note:

Viscoelastic haemostatic assays have emerged as a popular rapid point-of-care test to assess haemostasis in bleeding patients and serve to guide patient-tailored transfusion strategies. In this issue of Topical Update, Drs Joyce KWONG and Eudora CHOW share their valuable experience of using viscoelastic haemostatic assays to investigate and guide treatment in patients with challenging bleeding tendency. We welcome any feedback or suggestion. Please direct them to Dr Alvin IP, Education Committee, The Hong Kong College of Pathologists. Opinions expressed are those of authors or named individuals, and are not necessarily those of The Hong Kong College of Pathologists.

Introduction

Viscoelastic haemostatic assays (VHAs), particularly thromboelastography, have a rich history dating back to their introduction in 1948 - predating the development of the activated partial thromboplastin time (aPTT) test. Originally, VHAs were utilized as research tools to comprehensively assess the haemostatic competence of whole blood samples. This technology then found its way into clinical practice, first seeing widespread adoption in cardiac surgery in late 1950s, and later during orthotopic liver transplantation procedures. Over the course of subsequent decades, VHAs have gained increasing attention as essential tools for goal-directed haemostatic resuscitation of trauma-induced coagulopathies. In this article, we would share our experience in applying VHA to optimize patient management.

General Principles of Viscoelastic Haemostatic Assays

Viscoelasticity, a key principle of these assays, denotes the ability of certain materials, including blood, to exhibit both viscous and elastic characteristics during deformation. During the process of coagulation, blood undergoes significant changes, transitioning from a viscous to an elastic state. The resultant complex clot structure enables clot to resist deformation under shear forces, measured by the elastic shear stiffness of a material known as shear modulus. Even though

the term “clot strength” is used frequently in VHA systems, clot stiffness is measured either indirectly or directly. In various devices, such as TEG® 5000, ROTEM® delta and ClotPro®, shear modulus is assessed indirectly by submerging a pin in whole blood, whereas in Quantra®, it is assessed directly with sonographic method. A variety of activators are used for each device to examine different aspects of the haemostatic system and, as the blood clots, a graphical representation is made.

The normal TEG® / ROTEM® Tracing

At the beginning of the TEG®/ROTEM® tracing, no torque between the pin and the cup is transmitted producing two superimposed flat lines. When the blood starts clotting, the two lines progressively diverge until the maximal clot firmness is reached. Then, the lines start converging again as a result of clot lysis. The tracing has been traditionally described as having a ‘glass of cognac’ appearance (Figure 1). Five standard measurements are usually derived from this tracing. The time it takes for the trace to reach 2 mm of amplitude is called the reaction time (R time) for TEG® and the clotting time (CT) for ROTEM®. This precoagulation zone provides information about thrombin generation prior to the deposition of fibrin strands. Circumstances leading to impaired thrombin generation, such as clotting factor deficiencies and treatment with heparin or vitamin K antagonists, prolong this time. The time elapsed between 2 mm and 20 mm of amplitude is called the coagulation time (K time) for TEG® and the clot formation time (CFT) for the ROTEM®. The α angle (α) is most commonly defined as the angle formed by drawing a tangent line between the point where the two lines separate and the developing trace although other definitions have been used. The α angle and the K time or CFT provide information about how fast the clot forms and depend on clotting factors, platelets and fibrinogen level. The maximum clot firmness (MCF) for the ROTEM® and maximal amplitude (MA) for the TEG® correspond to the peak amplitude of the tracing and mainly depend on the platelets and the fibrinogen level. The amplitudes recorded after 5–10 min (A5-A10) are well correlated to the final clot firmness and therefore allows earlier decisions. Ly30 and Ly60 correspond to the percentage of reduction of the area under the TEG® curve observed, assuming a constant MA, at 30 and 60 min after MA is reached. For ROTEM®, the Clot Lysis Index at 30–60 min (CLI30-CLI 60) is the percent reduction in MCF observed 30–60 min after the CT. These latter parameters are used to quantify fibrinolysis.

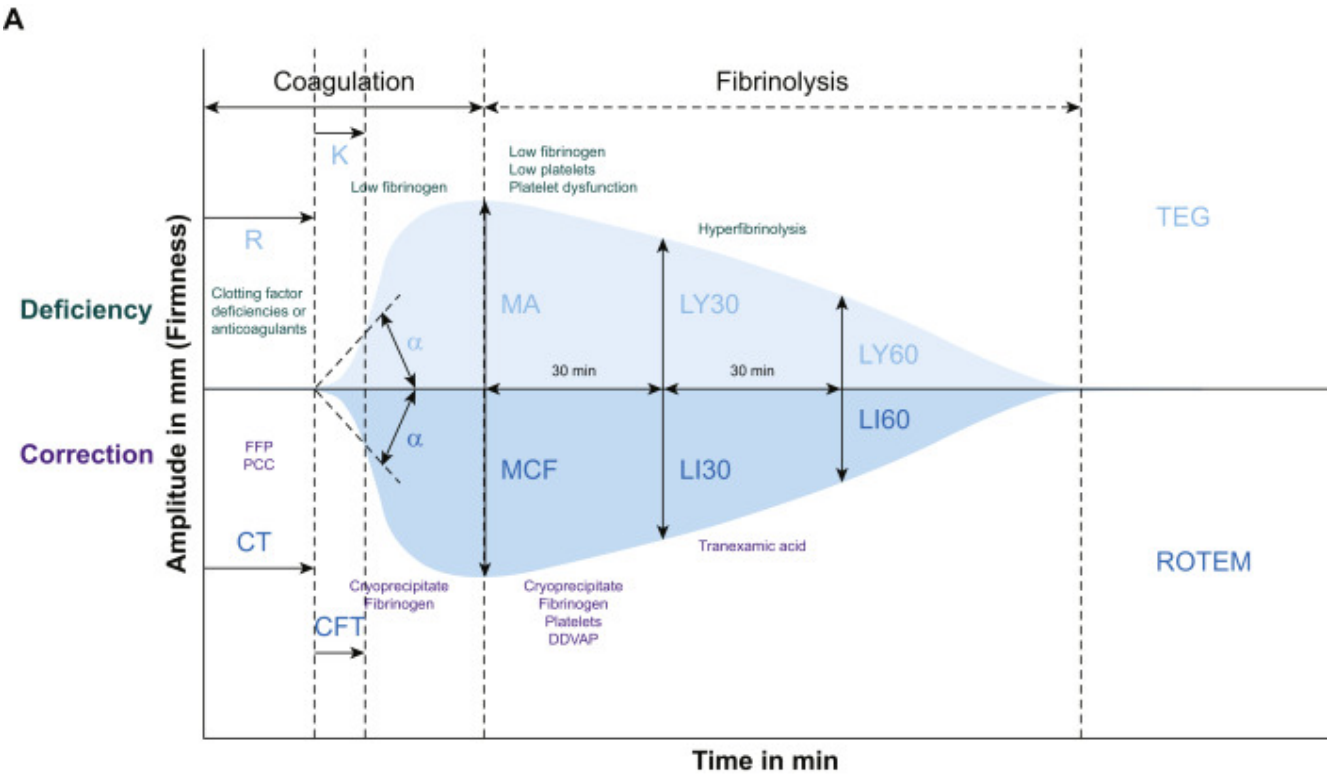

Figure 1. TEG® and ROTEM® traces. Typical tracing obtained with a viscoelastic clotting analyzer.

Pre-analytic Issues

Thromboelastography was originally described using fresh whole blood, the test being performed within 4–6 min after blood sampling. Using citrated blood allows the analysis to be delayed by up to several hours but produces slightly different results so that an appropriate reference range has to be used.

Comparison with Classical Clotting Assays

Compared to traditional clotting assays that utilize platelet-poor plasma (PPP), viscoelastic haemostatic assays are conducted using whole blood samples. This methodological distinction is crucial, as it enables VHAs to provide a real-time assessment of the entire coagulation process, incorporating the dynamic contributions of platelets, coagulation factors, and fibrinogen levels. The absence or dysfunction of any single component within this "haemostatic jigsaw" becomes quickly apparent, often within just 5 minutes of analysis. VHAs further complement this rapid detection capability by delivering detailed insights into the patient's fibrinolytic activity as well.

Local Experience in Application of Viscoelastic Haemostatic Assays

In our centre, viscoelastic haemostatic assays are mostly conducted in the Blood Bank. The results are displayed real time in operating rooms and intensive care units. This approach involves close collaboration between the attending surgeon, anaesthetist, and haematologists, ensuring optimal delivery of blood products and guidance on haemostatic resuscitation based on the clinical situation and VHA results.

Evaluation and management of bleeding in a patient with postpartum haemorrhage

Case 1

A 30-year-old woman underwent a caesarean section due to prolonged latent phase. The estimated blood loss during the procedure was less than 500mL. However, she experienced signs of shock 12 hours after the caesarean section, with haemoglobin level dropped to 6 g/dL. The platelet count was normal. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) were mildly prolonged to 17.5 seconds and 36.6 seconds, respectively. She received two units of red cells, and empirical tranexamic acid was given. An emergency laparotomy revealed 750mL of fresh blood and clots with slow oozing over the vesicouterine fold. Haemoperitoneum was drained, and local haemostatic measures were performed. To assess the coagulopathy, a viscoelastic haemostatic assay (ROTEM®) was promptly performed. Initial results (Figure 2) were available within 5 minutes, showed a significant decrease in FIBTEM A5 and maximum clot firmness (MCF), indicating hypofibrinogenaemia. To correct the coagulopathy, six grams of fibrinogen concentrates were administered. The targeted intervention achieved effective haemostasis, and no further blood transfusion was needed.

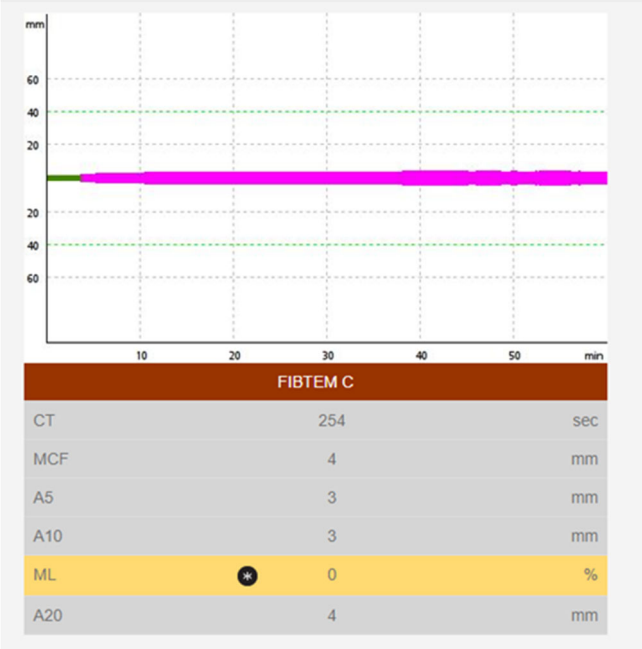

Figure 2. Hypofibrinogenaemia and / or disturbed fibrin polymerization in ROTEM® FIBTEM

Postpartum haemorrhage (PPH) remains the leading cause of preventable maternal morbidity and mortality worldwide. According to a study conducted in Hospital Authority Obstetric Units in 2013, massive primary PPH occurred in 0.76% of all deliveries, with the majority (84.1%) occurred after caesarean sections. Data from VHA studies have enhanced our understanding of the coagulation profiles of patients who experience PPH. VHA can rapidly identify the presence, type, and severity of PPH-associated coagulopathy, in order to facilitate targeted or “goal-directed” therapy. Multiple studies indicate that low fibrinogen level detected during the early phase of postpartum bleeding is strongly associated with progression to more severe PPH. In an observational study of 356 patients with PPH, those who required massive transfusion had a median serum fibrinogen level of 210 mg/dL and a median FIBTEM A5 of 12 mm. Notably, FIBTEM A5 was found to be predictive of the need for blood transfusion, invasive procedures, blood loss >2500 mL, duration of bleeding, and length of intensive care unit (ICU) stay.

Evaluation and management of bleeding in patients with acute bleeding

Case 2

A 73-year-old man, previously in good health, was admitted to the Emergency Department with sudden severe abdominal pain and haematemesis. He was in a state of haemorrhagic shock with BP 72/38 mmHg and a pulse rate 113 beats per minute. His initial haemoglobin level was 9.3 g/dL. The patient received fluid resuscitation and inotropic support. An urgent endoscopy revealed torrential bleeding from a duodenal ulcer, which was initially treated with adrenaline injection. Although this slowed the bleeding and briefly improved the patient's blood pressure, the bleeding resumed with fresh, spurting blood, and the patient went into cardiac arrest. Fortunately, spontaneous circulation returned after 1 minute of cardiopulmonary resuscitation. His haemoglobin level dropped to 3.7 g/dL. Platelet count was normal, but his PT and aPTT were prolonged to 22.6 seconds and 76.5 seconds respectively. Fibrinogen level was not checked at this stage. He received 4 units of red cells and 4 units of plasma. To guide the ongoing transfusion strategy, a viscoelastic haemostatic assay (ROTEM®) was promptly performed. The initial results (Figure 3), available at 10 minutes, indicated a significant decrease in FIBTEM A10 and maximum clot firmness (MCF), suggesting hypofibrinogenaemia. He was given fibrinogen concentrates and cryoprecipitate. Further analysis of the ROTEM® data revealed the maximum lysis (ML) was 100% which was indicative of exaggerated fibrinolysis (normal ML <15%). The lysis index at 45 and 60 mins were 75% and 16%, respectively (data not shown in Figure 3), indicating partial clot dissolution 45 minutes after initial clot formation. Consequently, tranexamic acid (1 gram) was administered based on the VHA results. Haemostasis was achieved, and no further blood transfusions were required.

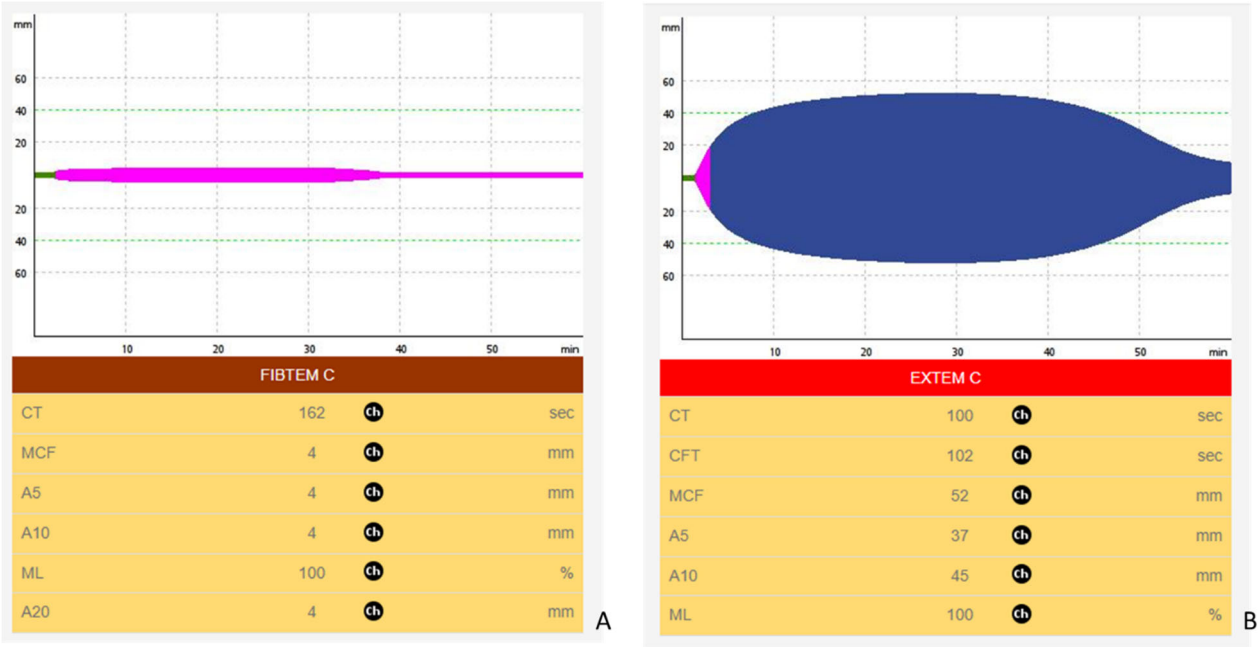

Figure 3. Combined hypofibrinogenaemia and / or disturbed fibrin polymerization and hyperfibrinolysis in (A) ROTEM® FIBTEM and (B) ROTEM® EXTEM.

Hyperfibrinolysis is a commonly overlooked cause of coagulopathy that can worsen with haemodilution and the loss of endogenous fibrinolysis inhibitors, such as plasminogen activator inhibitor-1. Unlike the CRASH trial, which emphasized the use of antifibrinolytic agents like tranexamic acid (TXA), the HALT-IT (Haemorrhage Alleviation With Tranexamic Acid -

Intestinal System) trial, a large international randomized controlled trial that assessed the effects of tranexamic acid in patients with gastrointestinal (GI) bleeding, showed no significant reduction in bleeding deaths with tranexamic acid. This has led to the suggestion that tranexamic acid should not be used as an empirical treatment for GI bleeding. Rapid recognition of hyperfibrinolysis is, therefore, crucial for guiding appropriate treatment. Diagnosing hyperfibrinolysis often proves challenging. Although several laboratory values can be used to measure fibrinolysis, such as euglobulin clot lysis time, plasmin-antiplasmin complex level, and plasminogen activator inhibitor-1 level, these are time-consuming and of limited availability in most clinical settings. In contrast, VHAs are able to provide a global assessment of coagulation and fibrinolysis within a clinically relevant time frame. This allows for the rapid identification of hyperfibrinolysis and guides targeted treatment. However, one of the limitations of standard VHA protocols, which utilize high tissue factor concentrations, is that they may only be sensitive to pronounced or exaggerated hyperfibrinolysis. More sensitive VHA protocols, such as those using lower tissue factor concentrations, may be required to detect milder degrees of increased fibrinolysis.

Evaluation and management of a patient after snakebite

Case 3

A 58-year-old man was admitted to the Emergency Department after being bitten by his pet snake, *Protobothrops magshanensis*. During the initial clinical examination, his right hand was swollen with mild oozing from the fang marks. Due to the extensive swelling, the patient received antivenom as an immediate treatment. Initial blood tests showed the patient had incoagulable state, with PT > 120 seconds, APTT > 180 seconds and undetectable fibrinogen level. Despite the abnormal coagulation parameters, the patient exhibited minimal bleeding symptoms, and no blood products were initially transfused. The following day, the swelling progressed to forearm and upper arm, with blisters, necrosis and suspected compartment syndrome. Aspiration of the blister was performed, but persistent oozing from the wound afterwards. The patient's haemoglobin level dropped to 6.3 g/dL. Viscoelastic haemostatic assay (ROTEM®) analysis showed no clot formation (Figure 4), indicating severe coagulopathy. In response, additional antivenom and vigorous transfusion were administered. Stable clot formation was finally observed on the 10th day of admission, but the coagulation profile remained abnormal, with prolonged clotting time (CT) on the EXTEM and FIBTEM assays.

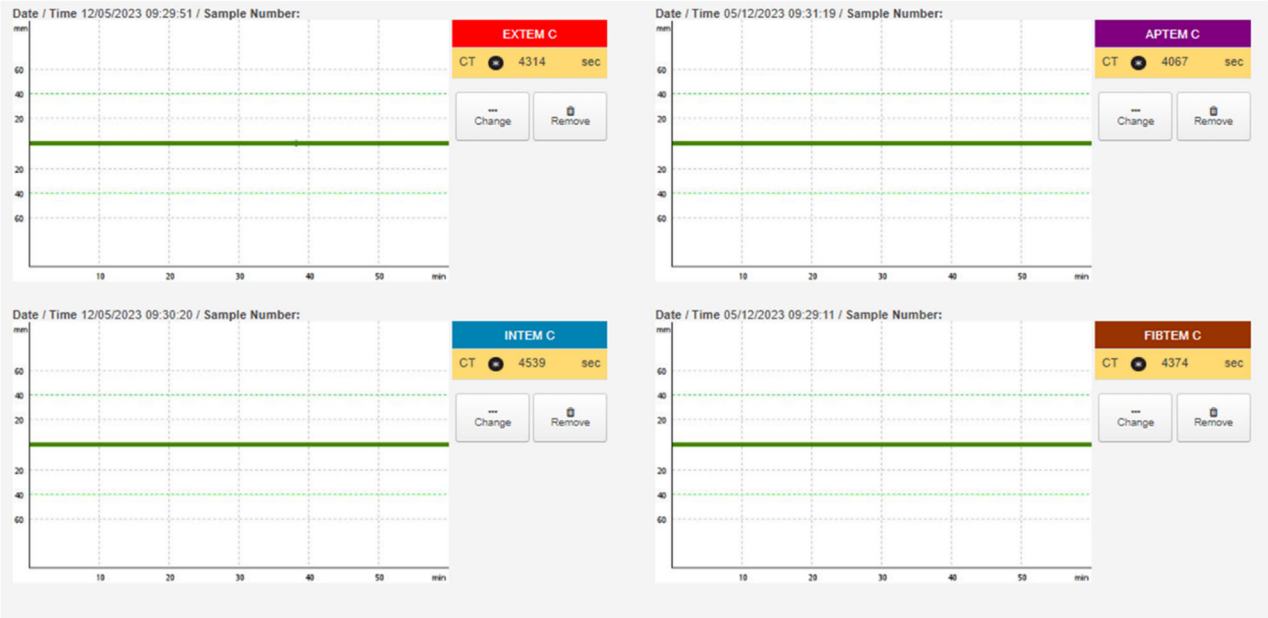

Figure 4. No clot formation on ROTEM®.

Venomous snake bites can be life-threatening with coagulopathy being the most common and clinically significant complication worldwide. Venom-induced consumption coagulopathy (VICC) is particularly concerning, as it can lead to potential fatal bleeding. There have been limited reports on the use of viscoelastic haemostatic assays (VHA) for the assessment and management of snakebite cases. One of the largest series comes from South Africa, where a study reviewed 51 cases utilizing thromboelastography (TEG®). The authors found that TEG® was a more accurate predictor of snakebite disease severity compared to using the international normalized ratio (INR) alone. In Vietnam, a prospective observational study involving 41 patients with viper envenomation further demonstrated the utility of rotational thromboelastometry (ROTEM®) in this setting. The study showed that ROTEM® could effectively detect a state of hypocoagulability in patients suffering from viper snakebites. These limited but important studies highlight the potential value of incorporating VHA in the assessment and management of snakebite-induced coagulopathy.

Conclusion

In summary, viscoelastic haemostatic assays have become integral tools in the assessment and management of patients with active bleeding. Firstly, VHAs provide real-time insights into the complex, dynamic process of coagulation. Furthermore, the comprehensive nature of VHAs enables more targeted and personalized transfusion strategies. By identifying specific coagulation factor deficiencies or imbalances, clinicians can tailor the administration of blood products, coagulation factor concentrates, and other haemostatic interventions. This precision-based approach helps to optimize the use of limited blood resources and improve patient outcomes.

References

1. Amgalan A, Allen T, Othman M, Ahmadzia HK. Systematic review of viscoelastic testing (TEG/ROTEM) in obstetrics and recommendations from the women's SSC of the ISTH. J Thromb Haemost. 2020;18(8):1813-1838.
2. Collins PW, Lilley G, Bruynseels D, et al. Fibrin-based clot formation as an early and rapid biomarker for progression of postpartum hemorrhage: a prospective study. Blood. 2014;124(11):1727-1736.
3. Curry NS, Davenport R, Pavord S, et al. The use of viscoelastic haemostatic assays in the management of major bleeding: A British Society for Haematology Guideline. Br J Haematol. 2018;182(6):789-806.
4. Dang XT, Nguyen TX, Nguyen HTT, Ha HT. Correlations between rotational thromboelastometry (ROTEM) and standard coagulation tests following viper snakebites. J Int Med Res. 2022;50(1)
5. Drotarova M, Zolkova J, Belakova KM, et al. Basic Principles of Rotational Thromboelastometry (ROTEM®) and the Role of ROTEM-Guided Fibrinogen Replacement Therapy in the Management of Coagulopathies. Diagnostics (Basel). 2023;13(20):3219.
6. Hadley GP, McGarr P, Mars M. The role of thromboelastography in the management of children with snake-bite in southern Africa. Trans R Soc Trop Med Hyg. 1999;93(2):177-179.
7. Hans GA, Besser MW. The place of viscoelastic testing in clinical practice. Br J Haematol. 2016;173(1):37-48.
8. Isbister GK. Procoagulant snake toxins: laboratory studies, diagnosis, and understanding snakebite coagulopathy. Semin Thromb Hemost. 2009;35(1):93-103.

9. Ker K, Mansukhani R, Shakur-Still H, Arribas M, Beaumont D, Roberts I. Tranexamic acid for gastrointestinal bleeding: can a reduction in the risk of death be discounted? A systematic review and meta-analysis of individual patient data from 64 724 bleeding patients. BMJ Open. 2023;13(2):e059982.
10. Leung WC. Prevention of postpartum haemorrhage. Hong Kong Med J. 2020;26(5):370-371.
11. Wang IJ, Park SW, Bae BK, et al. FIBTEM Improves the Sensitivity of Hyperfibrinolysis Detection in Severe Trauma Patients: A Retrospective Study Using Thromboelastometry. Sci Rep. 2020;10(1):6980.
12. Whiting, D. and DiNardo, J.A. TEG and ROTEM: Technology and clinical applications. Am. J. Hematol., 2014;89: 228-232.