Use of viscoelastic haemostatic assay in emergency and elective surgery

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A B S T R A C T

Objectives: To review the current evidence for the use of viscoelastic haemostatic assays in different surgical settings including trauma, cardiac surgery, liver transplantation, as well as the monitoring of antiplatelet agents and anticoagulants prior to surgery.

Data sources: PubMed database.

Study selection: Key words for the literature search were "thromboelastography" or "ROTEM" in combination with "trauma", "antiplatelet", "cardiac surgery", "liver transplantation" or "anticoagulants".

Data extraction: Original and major review articles related to the use of viscoelastic haemostatic assays.

Data synthesis: Haemostatic function is a critical factor determining patient outcomes in emergency or elective surgery. The increasing use of antiplatelet agents and anticoagulants has potentially increased the risks of haemorrhages and the need for transfusion. Conventional coagulation tests have limitations in detecting haemostatic dysfunctions in subgroups of patients and are largely ineffective in diagnosing hyperfibrinolysis. The viscoelastic haemostatic assays are potentially useful point-of-care tools that provide information on clot formation, clot strength, and fibrinolysis, as well as to guide goal-directed transfusion and antifibrinolytic therapy. They may also be used to monitor antiplatelet and anticoagulant therapy. However, standardisation of techniques and reference ranges is required before these tests can be widely used in different clinical settings.

Conclusions: Viscoelastic haemostatic assays, as compared with conventional coagulation tests, are better for detecting coagulopathy and are the only tests that can provide rapid diagnosis of hyperfibrinolysis. Goal-directed administration of blood products based on the results of viscoelastic haemostatic assays was associated with reduction in allogeneic blood product transfusions in trauma, cardiac surgery, and liver transplantation cases. However, there is currently no evidence to support the routine use of viscoelastic haemostatic assays for monitoring platelet function prior to surgery.

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Introduction

Conventional coagulation tests (CCTs) including prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen level, and D-dimer have long been the standard laboratory indicators of patients' coagulation status. With the introduction of the cell-based model of haemostasis,[1] the role of platelets for intact thrombin generation, and the limitations of CCTs have become increasingly recognised. First of all, CCTs only measure individual clotting components but do not take into account the important interactions between platelets, clotting factors, and other cellular components in the generation of thrombin, nor the balance between coagulation and fibrinolysis. Consequently, results from CCTs may not correlate with clinically significant coagulopathies or guide transfusion. Secondly, the quantity of individual elements does not necessarily indicate how well haemostasis is functioning, and qualitative dysfunction of platelets and clotting factors is not taken into account. In addition, PT/aPTT do not assess the overall strength and stability of clots as they are read at the initiation of fibrin polymerisation, which occurs when only <5% of total thrombin has been generated. Last but not least, CCTs are not point-of-care assays and the long processing time may lead to treatment delay with associated morbidity and mortality.[2]

In recent years, there has been an increasing use of viscoelastic haemostatic assays (VHAs), mainly thrombelastography (TEG; Hemoscope Corporation, Niles [IL], US) and the rotational thromboelastometry (ROTEM; Tem International GmbH, Munich, Germany), to provide global and

粘彈性止血測試於急性和非急性手術的應用

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目的：分析粘彈性止血測試在不同手術情況下使用的臨床證據，包括創傷、心臟手術、肝臟移植，以及在手術前用來監測血小板的功能和抗凝的情況。

資料來源：PubMed資料庫。

研究選取：用以搜索文獻的關鍵詞為「凝血彈性描記法」（thromboelastography）或「ROTEM」加上「創傷」（trauma）、「抗血小板」（antiplatelet）、「心臟手術」（cardiac surgery）、「肝臟移植」（liver transplantation）或「抗凝藥」（anticoagulants）。

資料提取：與粘彈性止血測試相關的論著和學術論文。

資料綜合：急性和非急性手術中止血是患者預後的關鍵因素。大量使用抗血小板和抗凝藥會增加出血的風險而須輸血。常規凝血測試來檢測止血功能障礙應用在一些患者群組中有局限性，並對於診斷纖維蛋白溶解過度基本上無效。粘彈性止血檢測對提供凝塊資料、凝塊強度和纖維蛋白溶解很有效，並替往後的輸血和抗纖溶治療提供指引。它們也可用於監測抗血小板和抗凝藥治療。然而，把這技術應用於不同的臨床情況之先，必須把所需的技術和參考範圍統一化。

結論：相比於傳統凝血測試，粘彈性止血測試較易分析凝血問題，而它也是現時唯一一個能快速偵測纖維蛋白溶解過度的測試。如果根據粘彈性止血測試的結果而提供特定的血液製品，可以減低在創傷、心臟手術和肝臟移植下使用異體移植的血液製品。然而，現今還未有證據支持在手術前廣泛使用粘彈性止血測試來監測血小板的功能。

functional assessment of coagulation. Both tests can be performed at the point-of-care during both emergency and elective surgery, and may be used to target transfusion at specific abnormalities with a positive impact on minimising unnecessary transfusion of allogeneic blood products.[3-5]

In the following sections, we shall describe the basic principles of VHAs, followed by a literature review of current evidence for its use. We searched the PubMed database for all original and major review articles published in the English language, using the keywords "thromboelastography" or "ROTEM" in combination with "trauma", "antiplatelet", "cardiac surgery", "liver transplantation" or "anticoagulants". Abstracts were screened for eligibility, and the reference lists of eligible articles were searched for further related studies. The date of the last search was 31 May 2013. All original studies and major review articles concerning the use of TEG and/or ROTEM in trauma, cardiac surgery, liver transplantation, and monitoring of antiplatelet agents and anticoagulants were included.

Principles of viscoelastic haemostatic assays

Thrombelastography was first described in 1948 by Hartert[6] as a method to assess the viscoelastic properties of coagulation in whole blood under low shear conditions. The VHAs give a graphic presentation of clot formation and subsequent lysis.[3] They measure the viscoelastic properties of a clot as it forms in a cup after the addition of activators. As the cup or pin oscillates, the torque of the rotational cup, which is directly related to the strength of the formed clot, is transmitted via the pin to a mechano-electrical transducer (Fig 1). The signals are then analysed by a computer that produces a trace graph. The latter is divided into several parts with each reflecting different stages of the haemostatic process (Fig 2). Although the nomenclatures differ between TEG and ROTEM, both provide information on the speed of coagulation initiation (coagulation factor activation), kinetics of clot growth (thrombin generation and cleavage of fibrinogen), clot strength, and fibrinolysis (Table). Different tracing morphology and parameters will indicate which component of the coagulation process may be dysfunctional.

Theoretical advantages of viscoelastic haemostatic assays over conventional coagulation tests

Viscoelastic haemostatic assays assess the combined influence of circulating plasmatic and cellular (platelets, erythrocytes, leukocytes, microparticles) elements. Results are available within 10 minutes, which can be utilised at the point-of-care in different

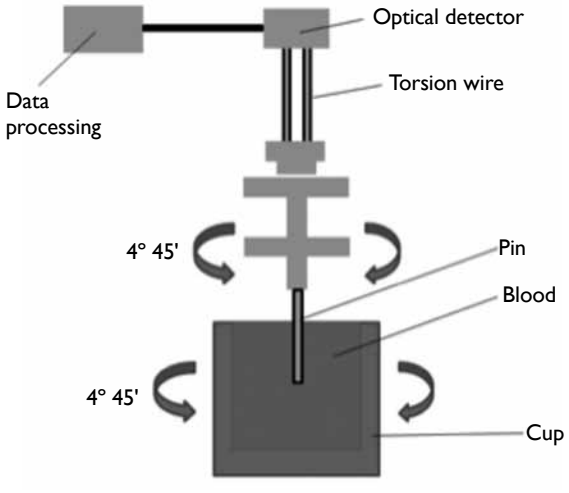

FIG 1. The principles of viscoelastic tests
Blood is incubated at 37°C in a heated cup. Within the cup is suspended a pin connected to a detector system (a torsion wire or an optical detector). The cup and pin are oscillated relative to each other through an angle of 4° 45'. The movement is initiated from either the cup or the pin. As fibrin forms between the cup and pin, the transmitted rotation from the cup to pin or the impedance of the rotation of the pin are detected, and a trace is generated

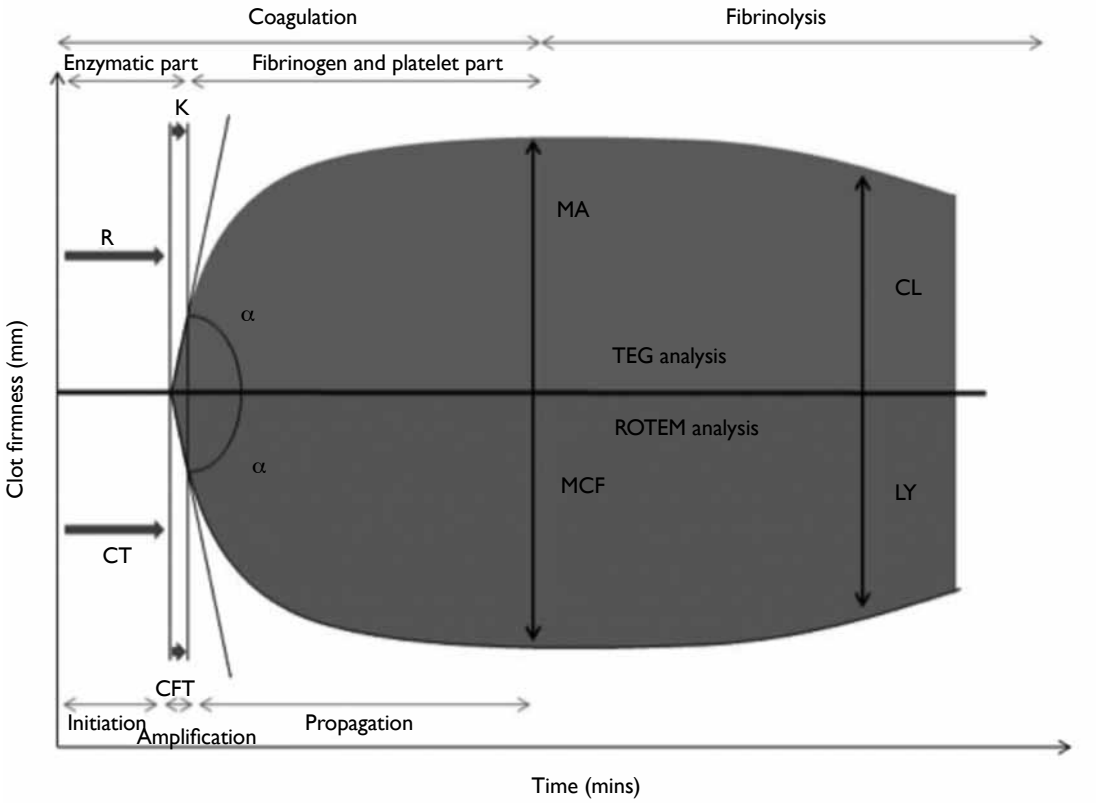

FIG 2. TEG and ROTEM tracing TEG parameters

Abbreviations: α = alpha angle; CFT = clot formation time; CL = clot lysis (for TEG analysis); CT = clotting time; K = kinetics; LY = clot lysis (for ROTEM analysis); MA = maximum amplitude; MCF = maximum clot firmness; R = reaction time; ROTEM = rotational thromboelastometry (Tem International GmbH, Munich, Germany); TEG = thrombelastography (Hemoscope Corporation, Niles [IL], US)

TABLE. TEG and ROTEM parameters and their meanings

TEG	ROTEM	Definition	Representative clotting process
R	CT	Time to 2 mm amplitude	Enzymatic clotting factor activation
K	CFT	Clot kinetics (time from 2 to 20 mm amplitude)	Thrombin's ability to cleave soluble fibrinogen
α	α	Slope between R and K	Rate of thrombin generation, which directly influences conversion of fibrinogen to fibrin
A (A30, A60)	A (A10, A15, A20, A25, A30)	Amplitude (at a fixed time)	Affected by fibrinogen, platelet (number and function) and factor XIII
MA	MCF	Maximal platelet-fibrin interaction via Gp IIb/IIIa receptors	
CL (Cl30, CL60)	LY (LY30, LY60)	% Of lysis at a certain time from MA	Antifibrinolytic activity such as plasminogen activation

Abbreviations: α = alpha angle; A = amplitude; CFT = clot formation time; CL = clot lysis (for TEG analysis); CT = clotting time; Gp = glycoprotein; K = kinetics; LY = clot lysis (for ROTEM analysis); MA = maximum amplitude; MCF = maximum clot firmness; R = reaction time; ROTEM = rotational thromboelastometry (Tem International GmbH, Munich, Germany); TEG = thrombelastography (Hemoscope Corporation, Niles [IL], US)

clinical settings. The end-points are clinically relevant, allowing goal-directed coagulation factor transfusions,[7-9] with a reduction in allogeneic blood product usage in trauma, cardiac, and liver surgery cases.[10-12] For example, fibrinogen concentrates could be given in situations with decreased maximum amplitude (MA)/maximum clot firmness (MCF). Last but not least, as fibrinolysis plays an important role in both trauma-associated coagulopathy as well as bleeding in patients undergoing elective cardiac and liver surgery, VHAs serve as the only tests available for rapid identification and quantification of hyperfibrinolysis in those situations.

Moreover, VHAs can be used in diagnosing surgical bleeding when the results of CCTs are normal, and also play an important role in the assessment of hypercoagulable states, prediction of bleeding risks in patients with liver and renal failures, and as a

research tool to improve the understanding of the impact of various interventions on coagulation.

Trauma surgery

Uncontrolled haemorrhage accounts for more than 50% of all trauma-related deaths within the first 48 hours after hospitalisation.[13-16] Current evidence suggests that haemodilution, hypothermia, acidaemia, and the consumption of clotting factors all play roles in the pathogenesis of coagulopathy in trauma.[17] Hyperfibrinolysis is associated with more severe injury, greater coagulation abnormalities, and a higher mortality rate. Kashuk et al[18] suggested that primary fibrinolysis occurred early in severely injured patients, leading to rapid clot dissolution.

Massive transfusion of blood products in trauma is not without risks, and may be associated with increased risks of acute respiratory distress syndrome, multi-organ failure, volume overload, and transfusion-related infections. In particular, the risk of transfusion-related acute lung injury following fresh frozen plasma transfusion is recognised as the most important cause of transfusion-associated mortality and morbidity.[19] Currently, the decision of what, when, and how much blood products to transfuse in massive trauma-related bleeding is mainly empirical, though often supplemented by results from CCTs. The laboratory diagnosis of fibrinolysis, unfortunately, is often a difficult one, requiring multiple tests such as euglobulin lysis time (ELT), platelet count, fibrinogen, protein S, protein C, and antithrombin levels, all of which may not be readily available in the acute phase of trauma management. Moreover, D-dimer (a marker of fibrinolysis) is elevated in virtually all trauma patients and is, therefore, not a useful indicator.

The VHAs, on the other hand, may provide distinct advantages by promptly diagnosing trauma coagulopathy (especially hyperfibrinolysis), guiding blood transfusions, and providing potential prognostic indicators. In a systematic review of 12 reported studies, Sankarankutty et al[20] found that TEG/ROTEM could be used to diagnose hyperfibrinolysis accurately. There were otherwise inconsistent correlations between VHAs and CCTs; the most consistent correlation identified was between TEG MA and ROTEM MCF with platelet count and aPTT. Davenport et al[21] showed that ELT, which was used as a gold standard test for the detection of fibrinolysis, was correlated with clot amplitude at 10 minutes and 15 minutes, MCF, and clot lysis index at 60 minutes. This has important implications in the use of antifibrinolytic agents and fibrinogen for targeted management.[22] As demonstrated in the CRASH-2 study, trauma patients who received an antifibrinolytic agent within 3 hours of trauma experienced a significant reduction in mortality.[23]

Other studies also provided evidence to support VHA-guided transfusion practice. Schöchl et al[24,25] reported that ROTEM-guided haemostatic therapy with coagulation factor concentrates (eg fibrinogen concentrate, prothrombin complex concentrate) could facilitate early and effective correction of coagulopathy, as well as reduce transfusion of allogeneic blood products. Kashuk et al[26,27] showed that goal-directed resuscitation based on rapid-TEG (rTEG) could reduce the use of fresh frozen plasma. In terms of prognostication, TEG MA and ROTEM MCF have been found to be associated with mortality, while excessive fibrinolysis diagnosed by either TEG clot lysis (CL) or ROTEM maximum lysis (ML) was an independent predictor of mortality.

Cardiac surgery

Heparin is used during cardiopulmonary bypass in open-heart surgery, and excessive postoperative bleeding has been attributed to the insufficient reversal of heparinisation with protamine sulfate. This is partly due to the fact that conventional monitoring by means of activated clotting time may fail to differentiate between the contributions from heparinisation, dilution, and platelet dysfunction.[28,29] Johansson et al[30] reviewed over 3250 cardiac patients reported in 16 studies, and demonstrated superiority of VHAs over CCTs in predicting bleeding and the need for re-operation. The total number of blood transfusions was reduced with VHA-guided transfusion compared with CCT-based practices. The degree of heparinisation could be evaluated with assays that neutralise the heparin (heparinase in TEG and HepTEM [heparinase-modified thromboelastometry] in ROTEM), so that non-heparin–related haemostatic problems could be detected. These findings were corroborated in a recent Cochrane analysis.[11]

Liver transplantation

A temporary hypercoagulable state is common after liver transplantation due to imbalance between the procoagulant and anticoagulant systems, as well as fibrinolytic shutdown.[31] This may play a role in the early development of hepatic artery thrombosis.[32] The use of CCT monitoring alone in the first week post-transplantation may lead to significant bleeding complications in certain patients.[33,34] In contrast, VHAs can accurately assess postoperative hypercoagulability and thrombosis. Cerutti et al[35] showed that TEG monitoring could demonstrate hypercoagulability in the majority of the subjects after living donor liver transplantation and may, therefore, be used to guide antithrombotic treatment in the perioperative period.

Monitoring antiplatelet therapy

With the rising prevalence of atherosclerotic

diseases such as ischaemic heart disease and stroke, it is not uncommon for surgical patients to be on antiplatelet drugs. The latter may worsen bleeding in trauma, increase transfusion requirement, and increase the need for re-operation after elective surgery.[36,37] Unfortunately, CCTs do not test for platelet inhibition due to antiplatelet therapy, and tests for platelet function such as platelet aggregometry do not provide results rapidly enough for intra-operative monitoring and assessment of coagulopathy in emergency surgery. Furthermore, although antiplatelet drugs are thought to work primarily by decreasing platelet aggregation, they may also have anticoagulant effects.[36] In this respect, the MA/MCF from TEG/ROTEM may serve to reveal the overall platelet function and fibrinogen levels. In differentiating whether reduced clot strength is due to low fibrinogen or low platelet concentration/functionality, both TEG and ROTEM have specific assays (functional fibrinogen and FIBTEM [fibrin-based clotting], respectively) that block platelet contributions with the addition of platelet inhibitors. At present, however, there is no clinical evidence to support the routine use of VHAs for monitoring platelet function prior to surgery. Further studies are required to demonstrate the clinical benefits of these tests in reducing transfusion requirement and improving surgical outcomes.

Monitoring anticoagulation therapy

Anticoagulation therapy has similar negative impact on emergency and elective surgery as antiplatelet therapy. Point-of-care VHAs have been shown to be useful in monitoring treatments with low-molecular-weight heparin (LMWH), heparinoids (eg danaparoid), and unfractionated heparin.[38] However, to increase the sensitivity of VHAs for the effects of LMWH and heparinoids, both standard and heparinase-modified tests have to be carried out. Recently, direct thrombin inhibitors such as dabigatran are being used increasingly for the prevention and treatment of venous thromboembosis, acute coronary syndrome, and heparin-induced thrombocytopenia.[39] The monitoring of this group of patients is facilitated by VHAs with the use of ecarin clotting time, in which ecarin is used to activate thrombin directly.[40,41]

Limitations of viscoelastic haemostatic assays

There is at present a lack of universally agreed algorithms for the use of VHAs. In a recent systematic review of nine randomised clinical trials (eight in cardiac surgery and one in liver transplantation) comparing VHA-based algorithms with standard treatments, the only supporting evidence identified for the use of VHAs was for detection of hyperfibrinolysis.[42]

On an operational level, VHAs have been criticised for not having undergone the same evaluation process as CCTs. There are wide technical variations in how VHAs are performed, and the machine requires calibrations 2 to 3 times a day which causes significant inconvenience in daily point-of-care usage.[42] While originally designed for fresh whole blood with no additional activators, subsequent modifications have included sample anticoagulation and the use of different activators to standardise the initiation of coagulation. Patients' gender, age, and alcohol drinking may also affect the result. Moreover, the normal reference ranges for VHAs were derived from hospitalised surgical patients in one study, and from a small sample of 12 healthy volunteers in another.[43] Hence, each centre is recommended to generate its own reference range by specially trained personnel according to the guidelines from the Clinical Laboratory Improvement Amendments.[44] The latter, which regulates all laboratory tests in the United States, demands a minimum of 30 to 40 subjects for special coagulation tests.[45] All these necessitate an active and tightly controlled quality assurance programme.[42]

Despite its proposed role as a point-of-care test, a complete viscoelastic test can take up to 60 minutes although useful information can be obtained in approximately 10 minutes, when MCF is reached. This may be further increased by a 30- to 40-minute wait for anticoagulated samples.[42] To compensate for this, a modified rTEG has been developed. It uses tissue factors as activators in addition to kaolin, and can provide results on MCF more rapidly. However, information on coagulation and clot formation time is limited. Although there is a strong correlation between rTEG and conventional TEG in terms of overall clot strength and platelet function, there is only moderate correlation in the degree of fibrin cross-linking and poor correlation in evaluating thrombolysis.[46]

There are conditions in which VHAs may fail to detect haemostatic dysfunction. The test setting is at 37°C. Therefore, the effect of hypothermia, which has a well-recognised negative impact on coagulation, may not be recognised.[47,48] Viscoelastic haemostatic assays do not assess the endothelial contribution to haemostasis since an activator is directly added to initiate coagulation during the test. This means that the diagnosis of certain conditions such as von Willebrand disease is not possible with VHAs.[48]

Lastly, the interchangeability of results between TEG and ROTEM has been questioned. Although they share the same fundamental principles, and similar parameters, hardware and techniques, the results generated may not be directly comparable,

possibly due to the use of different activators. Consistent correlations are limited to that between TEG MA and ROTEM MCF measurements, and that between TEG CL and ROTEM ML in diagnosing hyperfibrinolysis and predicting mortality.

Conclusions

Haemostatic function is a critical factor determining patient outcomes in emergency or elective surgery. The increasing use of antiplatelet agents and anticoagulants has potentially increased the risks of haemorrhages and need for transfusion. Conventional coagulation tests have limitations in detecting haemostatic dysfunction in subgroups of patients and are largely ineffective in diagnosing hyperfibrinolysis. The VHAs are potentially useful point-of-care tools to provide information on clot formation, clot strength, and fibrinolysis, as well as to guide goal-directed transfusion and antifibrinolytic therapy. They may also be used to monitor antiplatelet and anticoagulant therapy. However, standardisation of techniques and reference ranges is required before these tests can be widely used in different clinical settings. Further studies are needed to validate different algorithms, and address coagulopathies in situations like hypothermia or endothelial dysfunction.

Declaration

No conflicts of interest were declared by the authors.

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