A clinician's guide to viscoelastic testing in the perioperative period

Viscoelastic tests provide a global and dynamic assessment of the coagulation system and thus are becoming increasingly relied upon in the perioperative period. Many clinicians are unfamiliar with viscoelastic testing, so this article provides an overview of their use and interpretation in the management of perioperative bleeding.

In the perioperative period it is important to be able to accurately evaluate the coagulation system in real time, especially in surgery associated with a high risk of bleeding and ongoing coagulatory changes. While standard laboratory-based plasma coagulation tests, such as prothrombin time/international normalized ratio and activated partial thromboplastin time are available, these investigations have a number of limitations in the perioperative period (Hass et al, 2014). These tests are only reflective of certain parts of the haemostatic pathway. They do not provide information about overall coagulatory function. Additionally, these tests were designed predominantly to monitor anticoagulation therapy with warfarin and heparin. Indeed, there is little evidence to support the use of these tests for the diagnosis and treatment of perioperative bleeding or coagulopathy (Hass et al, 2014). Another major limitation with the use of conventional tests of coagulation in the perioperative period is the turnaround time for results, which can be greater than an hour. This often leads to the treatment of coagulopathy being based on clinical judgement using empirical protocols rather than on real-time information. This can result in higher surgical re-exploration rates and increased and unnecessary transfusions, leading to greater morbidity and mortality (Mallett and Armstrong, 2015).

Point-of-care testing is a solution to these issues by providing rapid coagulation results at 'the bedside'. A number of point-of-care tests exist, including prothrombin time/international normalized ratio, activated partial thromboplastin time, activated clotting time, thrombin time, platelet function and viscoelastic tests. Viscoelastic tests provide a global, dynamic assessment of clot kinetics, strength, stability and dissolution (Whiting and DiNardo, 2014). They offer the closest approximation to the complex process of the currently accepted cell-based model of haemostasis (Hoffman and Monroe, 2001; see *Table 1*).

This article provides an overview of the use and interpretation of viscoelastic tests in the management of perioperative bleeding, focusing on the two most commonly used viscoelastic tests in current clinical practice:

1. Thromboelastography (TEG; Hemonetics Corporation, Braintree, MA, USA)
2. Thromboelastometry (ROTEM; TEM International GmbH, Munich, Germany).

The principles of viscoelastic tests

Viscoelastic tests analyse overall clot development in real time and provide information on the interplay between clotting factors, fibrinogen, platelets and fibrinolytic agents. Both require a small volume of arterial or venous blood from the patient being tested.

Thromboelastography

The TEG device (*Figure 1*) consists of a cup which requires a 0.34 ml sample of the patient's blood. Thromboelastography currently requires a manual pipetting technique to put the exact amount of blood into the device cups, which can be subject to errors if the operator

Table 1. The cell-based model of haemostasis

Phase 1: Initiation	Activation of the clotting cascade when plasma is exposed to tissue factor following blood vessel damage
Phase 2: Amplification	Activation of platelets at the site of vascular injury to produce a platelet plug. The initial generation of thrombin results from activation of the clotting cascade
Phase 3: Propagation	Interaction of numerous clotting factors on the activated platelet surface results in a 'thrombin burst.' This facilitates the formation of a strong fibrin clot to achieve haemostasis
Phase 4: Termination	Anticoagulant factors inhibit the clotting cascade and clot removal occurs by fibrinolysis

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is inexperienced (Whiting and DiNardo, 2014). The cup with the blood sample oscillates every 5 seconds and a pin suspended in the blood sample by a torsion wire is connected to a mechanical-electrical transducer and subsequent display unit. Once a clot starts forming (initiation phase of coagulation) the pin becomes linked to and thus moves with the cup. As clot strength increases (amplification and propagation phases) the magnitude of the pin's motion also rises. However, once clot lysis begins (termination phase) the degree of pin motion falls. A transducer is able to convert the motion of the pin into an electrical signal that can be displayed graphically in real-time (Ganter and Hofer, 2008).

A newer version of TEG, TEG 6, which has just been released, will allow blood samples to be placed straight into cartridges and then analysed by the TEG device, removing the need for manual pipetting and any associated operator error. It has four channels, allowing multiple simultaneous assays to be performed, and operates using resonance technology rather than pin motion measurement.

Thromboelastometry

With the ROTEM device, the pin oscillates through the application of a constant force and the blood sample remains stationary. As the clot forms the motion of the pin is impeded. This is detected optically and converted to an electronic display. ROTEM can perform four analyses simultaneously and the new ROTEM Sigma only requires a single blood sample for all four analyses, minimizing operator intervention.

With both tests meaningful information on clot kinetics and strength can be obtained within 10 minutes but the whole assay takes up to 60 minutes (da Luz et al, 2013). The cost of running these tests is dependent on a number of factors including pricing from the manufacturers. Jackson et al (2009) provide an overview of the expected running costs of both these tests. Up to date pricing is available directly from the manufacturer.

Both TEG and ROTEM use different reagents to provide additional information on haemostasis (*Tables 2* and *3*).

Figure 1. The TEG 5000 Analyser.

How to interpret the results

The results of viscoelastic tests are displayed graphically, with amplitude of detector motion plotted

Table 2. Types of thromboelastography (TEG) assays

Test	Reagent (function)	Rationale
Native	None	Overall coagulation assessment
Kaolin	Kaolin (intrinsic pathway activator via factor XII)	Overall coagulation assessment (kaolin initiates haemostasis so results are faster than the native test)
Kaolin TEG with heparinase	Kaolin and heparinase (inactivates heparin)	Assess the impact of endogenous heparinoids and heparin on coagulation
Rapid TEG	Kaolin and tissue factor (extrinsic pathway activator via factor VII)	Accelerates the overall process to more rapidly assess coagulation, specifically clot strength and maximum amplitude
Functional fibrinogen	Tissue factor and abciximab (platelet glycoprotein 2b/3a inhibitor)	By inhibiting platelet function, the contribution of fibrinogen to maximum amplitude can be assessed and a value obtained for fibrinogen level
Platelet mapping	Four simultaneous TEG channels 1) Kaolin TEG 2) Activator F (reptilase and factor XIIIa) + heparin 3) ADP + heparin 4) Arachidonic acid + heparin	This assay evaluates the effect of antiplatelet drugs (aspirin and clopidogrel) on platelet function: Heparin suppresses thrombin generation Reptilase converts fibrinogen to fibrin and factor XIIIa cross-links fibrin Adenosine diphosphate (ADP) and arachidonic acid are platelet activators

Table 3. Types of ROTEM assays

Test	Reagent (function)	Rationale
NATEM	None	Non-activated assay, can be used to perform customized coagulation tests
INTEM	Phospholipid and ellagic acid (intrinsic pathway activator)	Coagulation assessment following intrinsic pathway activation (more sensitive to heparin and intrinsic pathway factor deficiencies)
EXTEM	Tissue factor (extrinsic pathway activator)	Coagulation assessment following extrinsic pathway activation (more sensitive to extrinsic pathway factor deficiencies)
HEPTEM	INTEM reagent and heparinase (inactivates heparin)	Assess the impact of endogenous heparinoids and heparin on coagulation
APTEM	EXTEM reagent and aprotinin (inhibits fibrinolysis)	Identifies hyperfibrinolysis
FIBTEM	EXTEM reagent and cytochalasin D (platelet inhibitor)	By inhibiting platelet function the sole contribution of fibrinogen to coagulation can be assessed

against time. A number of parameters are quantified that correspond to various parts of the haemostatic process and are thus influenced by differing physiological factors. These are summarized in *Figure 2* and *Table 4*.

Significance of a normal result

In patients with active bleeding during or after surgery, a normal viscoelastic test profile is very important in ruling out a coagulopathy as the underlying cause. This suggests a surgical cause for the haemorrhage is more likely (Mallett and Armstrong, 2015). However, with active bleeding coagulatory changes are dynamic and an initially normal coagulation profile may change as bleeding continues. This highlights the importance of regularly checking coagulation status and the benefits of using viscoelastic tests over conventional testing.

Deficiency in clotting factors

If coagulopathy is the result of a deficiency in procoagulant factors, such as factors II, V, VII, VIII, IX or X, the following abnormality is seen in the viscoelastic test trace. The reaction time (R) time on a kaolin TEG or the clotting time (CT)on ROTEM will be prolonged (*Figure 3a*). The treatment is to replace these factors by transfusing with fresh frozen plasma or prothrombin complex concentrate, following which these parameters should correct.

Excess heparin (an anticoagulant inhibiting factor IIa and Xa) or an increase in endogenous heparinoids will also result in a prolonged reaction time or clotting time. In order to distinguish a clotting factor deficiency from excess heparin the kaolin TEG and ROTEM INTEM can be run with heparinase. As this enzyme inactivates heparin, a subsequent correction in the reaction time or

Figure 2. a. Depiction of ROTEM analysis. b. Depiction of TEG analysis. A10 = clot amplitude at 10 minutes.

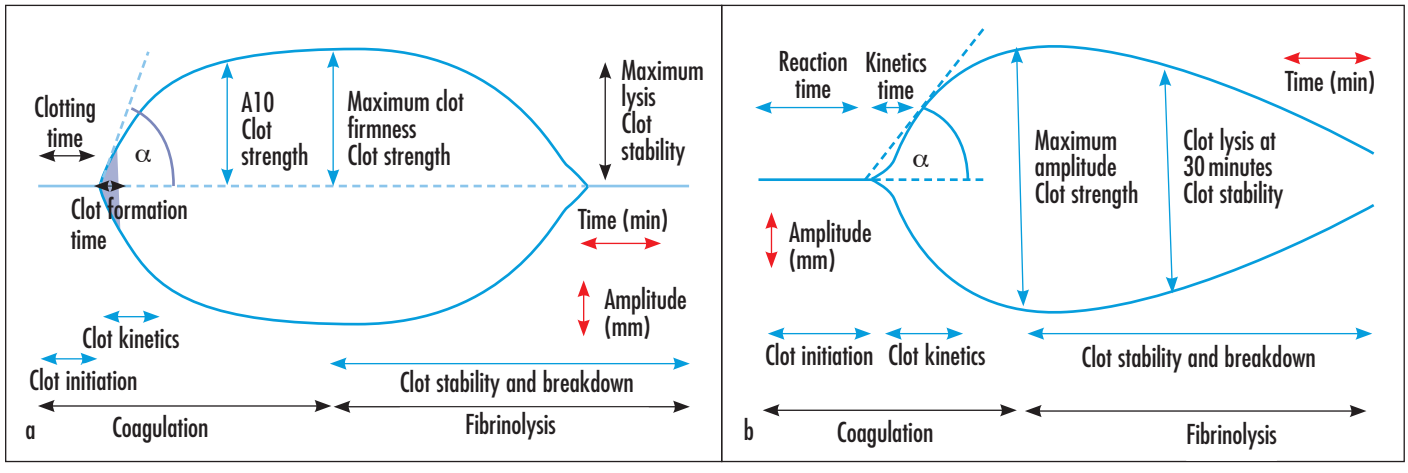


Table 4. Summary of TEG and ROTEM parameters

TEG parameters	Normal range (kaolin TEG)	ROTEM parameters	Normal range (INTEM)	Significance
R (reaction time) – time taken for clot amplitude to reach 2 mm	4–9 minutes	CT (clotting time) – time taken for clot amplitude to reach 2 mm	100–240 seconds	Measure of time taken to initiate coagulation. Influenced by pro- and anticoagulants. Prolonged in the presence of heparin or by low clotting factor activity
K (kinetics time) – time taken for clot amplitude to rise from 2 mm to 20 mm	1–3 minutes	CFT (clot formation time) – time taken for clot amplitude to rise from 2 mm to 20 mm	30–110 seconds	Measure of time taken to achieve certain clot strength. Reduced value if thrombin generation is impaired (anticoagulants, low clotting factor levels, low platelet count)
α (alpha angle) – angle formed by tangent to trace at 20 mm and the horizontal	59–740	α (alpha angle) – angle formed by tangent to trace at 20 mm and the horizontal	70–830	Measure of coagulation kinetics: low angle if poor thrombin generation, reduced platelet–fibrinogen interaction
		A10 – clot amplitude at 10 minutes after clotting time	44–66 mm	Measure of clot strength. Influenced by platelets and fibrinogen
MA (maximum amplitude) – peak amplitude of clot	55–74 mm	MCF (maximum clot firmness) – peak amplitude of clot	50–72 mm	Measure of clot strength. Influenced by platelets and fibrinogen
LY30 (lysis at 30 minutes) – percentage reduction in area under the curve 30 minutes after maximum amplitude	<7.5%	MI (maximum lysis) – maximum percentage reduction in maximum clot firmness, usually taken 60–90 minutes after clotting time	<15%	Measure of clot stability. Influenced by the degree of fibrinolysis

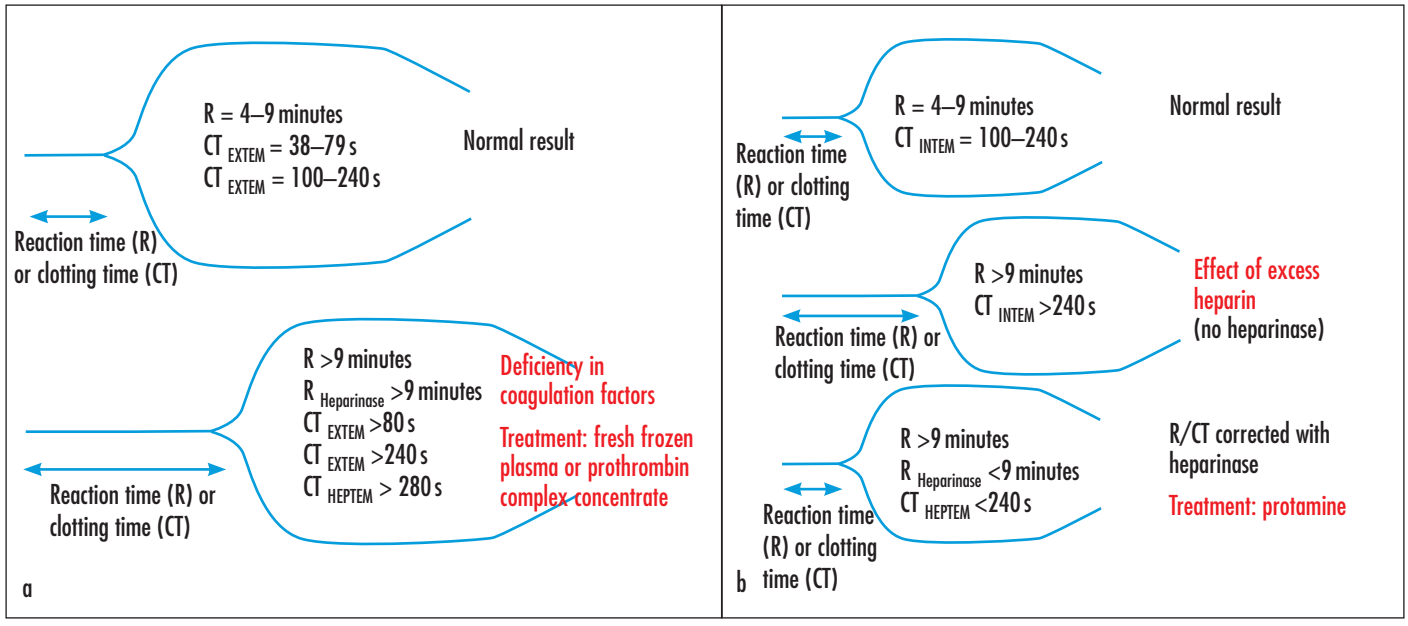


Figure 3. a. Deficiency in clotting factors. b. Effect of excess heparin.

clotting time suggests that the coagulopathy is caused by excess heparin (*Figure 3b*). This is an important distinction given the different treatments – protamine for excess heparin *vs* clotting products for a coagulation factor deficiency. In bleeding during cardiac surgery, for example, when heparin is used for cardiopulmonary bypass it is necessary to be able to differentiate heparin-induced coagulopathy from a clotting factor deficiency (Gorlinger et al, 2013).

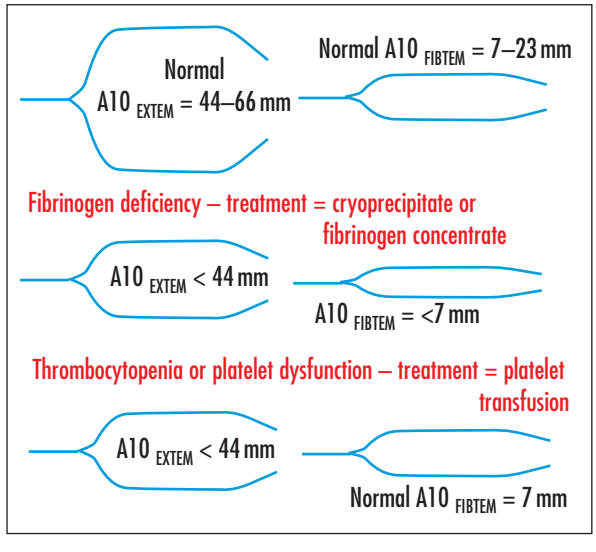
Platelet dysfunction and fibrinogen deficiency

A fibrinogen deficiency or platelet dysfunction can also lead to perioperative haemorrhage. On viscoelastic tests clot strength is determined by platelet number and the fibrinogen level (i.e. the maximum amplitude on TEG or clot amplitude at 10 minutes after clotting time (A10) of maximum clot firmness on ROTEM). Any impairment in either will result in a reduction in these parameters (*Figure 4*). When a decrease in clot strength is noted on viscoelastic tests, a functional fibrinogen assay on TEG and FIBTEM on ROTEM can be performed to distinguish between a platelet or fibrinogen problem. In such assays, a platelet inhibitor is added to ascertain the sole contribution of fibrinogen to clot strength. As *Figure 4* demonstrates if clot strength (evidenced here by A10 on ROTEM) is reduced on both EXTEM (not fibrinogen specific) and FIBTEM (fibrinogen specific) assays, then a fibrinogen deficiency is likely. Treatment can be with cryoprecipitate or fibrinogen concentrate. However, if A10 is reduced on EXTEM but normal on FIBTEM, then the reduction in clot strength is more likely to be the result of a platelet abnormality. Appropriate treatment may therefore be a platelet transfusion. Importantly, it is not possible to assess platelet function in patients on antiplatelet therapy with aspirin or clopidogrel using standard viscoelastic tests. It is necessary to use a modification of the TEG assay (platelet mapping) or another platelet function monitor, such as Multiplate.

Hyperfibrinolysis

Hyperfibrinolysis (over-activation of the fibrinolytic system resulting in rapid clot breakdown) is another cause of coagulopathy-induced bleeding. Viscoelastic tests have an advantage over conventional coagulation tests in being able to assess fibrinolytic activity by measuring clot stability over time. On TEG, the clot lysis at 30 minutes reflects the degree of clot lysis; if over 7.5% hyperfibrinolysis exists. The corresponding parameter on ROTEM is maximum lysis with the normal range being less than

Figure 4. Platelet dysfunction and fibrinogen deficiency. A10 = clot amplitude at 10 minutes.



15%. With ROTEM, an APTEM assay can also be performed when the maximum lysis is increased on the native or EXTEM (*Figure 5*). In an APTEM assay a reagent that inhibits clot breakdown is added and a subsequent correction in the maximum lysis confirms the existence of hyperfibrinolysis. Treatment involves administration of antifibrinolytic agents such as tranexamic acid, and studies have shown their use reduces bleeding, transfusion requirements and mortality in cardiac surgery and trauma (Shakur et al, 2010; Gorlinger et al, 2013).

Hypercoagulable state

Thromboembolic events contribute substantially to perioperative morbidity and mortality. Viscoelastic tests can be used to identify patients that are hypercoagulable and thus at risk of such complications. For example, Hincker et al (2014) used preoperative ROTEM assays to successfully predict which patients were likely to develop a postoperative deep vein thrombosis or pulmonary embolism. As demonstrated in *Figure 6*, a reduction in the reaction time or clotting time and an increase in the maximum amplitude or maximum clot firmness are indicators of hypercoagulability.

Figure 5. Hyperfibrinolysis.

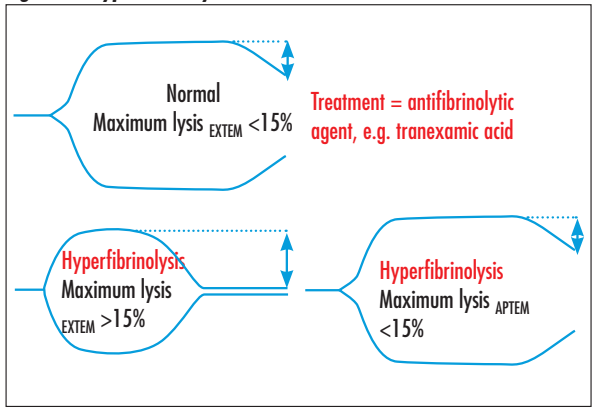
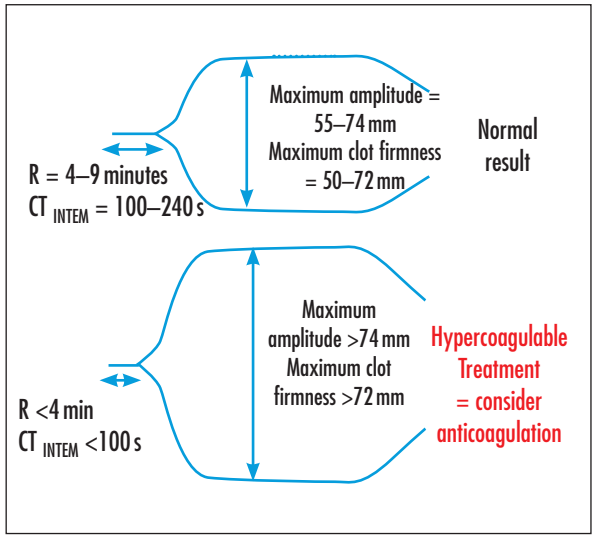


Figure 6. Hypercoagulable state. CT = clotting time; R = reaction time.



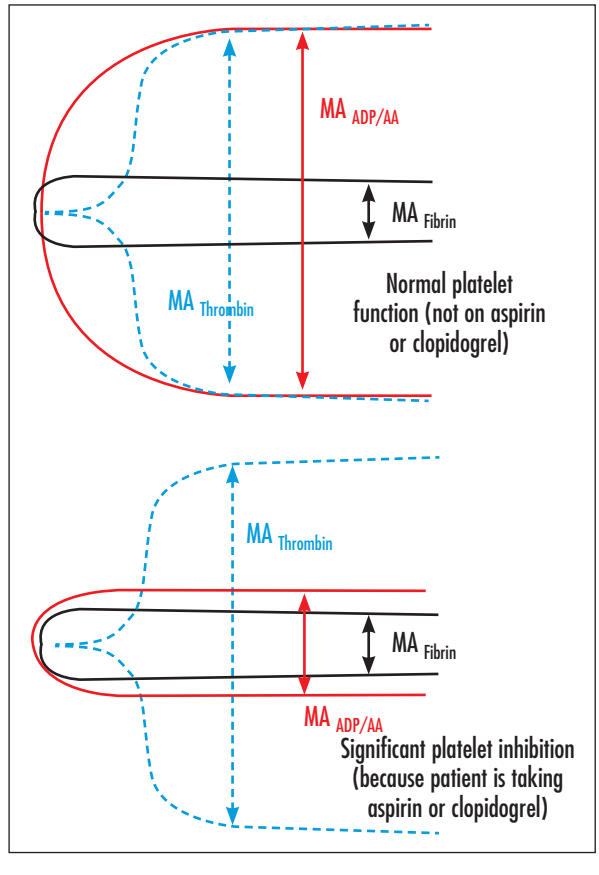
Platelet mapping

The TEG Platelet Mapping assay (Haemoscope Corporation, Niles, Illinois, US) measures the percentage platelet inhibition caused by antiplatelet agents (Collyer et al, 2009). Given the large number of surgical patients who are taking drugs such as aspirin and clopidogrel, it is important to be able to accurately assess their bleeding risk. The test involves four assays running simultaneously (*Table 2*), with maximum amplitude (MA) being the main parameter analysed. First, the kaolin TEG, which is unaffected by antiplatelet agents, measures maximal clot strength ($MA_{Thrombin}$). Second, activator F is added to a heparinised blood sample to isolate the contribution of fibrin to haemostasis (MA_{Fibrin}). Third, adenosine diphosphate is added to a heparinised blood sample to measure the decrease in clot strength caused by platelet inhibition by clopidogrel (MA_{ADP}). Fourth, arachidonic acid (AA) is added to a heparinised blood sample to calculate the decrease in clot strength as a result of platelet inhibition by aspirin (MA_{AA}). As *Figure 7* demonstrates, a reduction in $MA_{ADP/AA}$ occurs as a result of the action of clopidogrel or aspirin on platelet function.

The percentage platelet inhibition by each drug can be quantified by using the following mathematical formula (Bochsen et al, 2007).

% platelet inhibition = $100 - [(MA_{ADP/AA} - MA_{Fibrin}) / (MA_{Thrombin} - MA_{Fibrin}) * 100]$

Figure 7. Platelet mapping. AA = arachidonic acid; ADP = adenosine diphosphate; MA = maximum amplitude.



Thus an objective measure of the risk of bleeding for surgical patients who are taking antiplatelet agents can be obtained. Kasivisvanathan et al (2014) demonstrated that if patients on clopidogrel had an adenosine diphosphate receptor platelet inhibition percentage of less than 34%, it was safe for them to have their operation, on the basis that they were not at any greater risk of bleeding. Therefore, by identifying those on antiplatelet agents who are at low risk of perioperative haemorrhage, platelet mapping can help prevent unnecessary surgical cancellations.

Conclusions

Viscoelastic tests have value in the management of perioperative haemorrhage and coagulopathy. They allow clinicians to identify which aspects of the coagulation system are dysfunctional, thus enabling targeted therapy to be administered. Intraoperatively, coagulation deficits identified on viscoelastic tests should only be treated with haemostatic therapy if there is evidence of clinical bleeding. There is a growing body of evidence demonstrating the benefits of viscoelastic tests in cardiac, liver, trauma and obstetric surgery (Mallett and Armstrong, 2015). The data are strongest for cardiac surgery, with viscoelastic test-based transfusion algorithms shown to reduce perioperative transfusion requirements, decrease transfusion-related adverse events and improve 6-month mortality (Gorlinger et al, 2013). The advantage of such algorithms is that they provide clear, step-by-step instructions regarding the treatment of a bleeding patient depending on the results given by viscoelastic tests. Theusinger et al (2015) provide further evidence of the benefit of viscoelastic test-based algorithms to enable goal-directed therapy and limit the uncontrolled use of blood products in bleeding patients in cardiac, trauma and neurosurgery. The National Institute for Health and Care Excellence (2014) recommends the routine use of viscoelastic tests in high-risk cardiac surgery. It is important for clinicians involved in surgery with a high risk of haemorrhage and coagulopathy to be aware of the role of viscoelastic tests and interpretation of their results. **BJHM**

Figure 1, *the image of the TEG® 5000 Haemostasis Analyser, is used by permission of Haemonetics Corporation. The authors would like to thank Davis Bland, Haemonetics UK Ltd, for providing* Figure 1.

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Conflict of interest: none.

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KEY POINTS

- Point-of-care testing allows rapid results to be obtained, in the operating room, thus providing real-time information to enable clinicians to make accurate decisions.
- Viscoelastic tests provide a global, dynamic assessment of coagulatory function, offering much more information than conventional coagulation tests.
- In the context of perioperative bleeding, viscoelastic tests enable goal-directed therapy to be administered by identifying which aspects of the coagulation system are dysfunctional and thus need correcting.
- There is a strong evidence base supporting the use of viscoelastic tests, particularly in those surgeries where the risk of haemorrhage is high.

MANUFACTURERS' DETAILS

Thromboelastography (TEG; Hemonetics Corporation, Braintree, MA, USA). www.haemonetics.com/en/Products/Devices/Surgical%20-%20Diagnostic%20Devices/TEG%205000.aspx

Thromboelastometry (ROTEM; TEM International GmbH, Munich, Germany). www.rotem.de/en/products/rotem-delta/