Clinical aspects of coagulation and haemorrhage

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Abstract

Haemostasis is a complex physiological cascade that results in cessation of bleeding following injury. Inherited bleeding diatheses and hypercoagulable diseases remain a source of patient morbidity that should be recognized and managed. Liver disease should be seen as a heterogeneous group of disorders with unpredictable coagulation effects. The CRASH II trial, recent recommendation by the European Medicines Agency for re-licensing of Trasylol (aprotinin) and the increasing use of novel antiplatelet agents reflect the rapidly evolving haemostatic landscape. Empirical strategies for managing coagulopathy of any aetiology look increasingly flawed as the technology required to tailor therapy to individual situations is now widely available at the point of care.

Keywords Aprotinin; blood transfusion; coagulation tests; CRASH; disseminated intravascular coagulation (DIC); haemostasis; liver disease; platelets; point of care; thromboelastography (TEG)

Royal College of Anaesthetists CPD Matrix Code: 1A01, 1A02

Learning objectives

After reading this article, you should be able to:

- describe both laboratory and point-of-care coagulation tests
- describe acquired and inherited coagulation disorders
- discuss appropriate strategies to manage the bleeding patient
- explain when to use newer haemostatic agents and how they work

Haemostasis

Haemostasis is a complex physiological cascade with multiple checks and balances that results in cessation of bleeding following injury. During surgery there are multiple potential causes of haemostatic derangement; an effective perioperative (and indeed prehospital) clinician needs a clear understanding of the coagulation tests available and the treatment options available.

Tests of coagulation

Conventional coagulation tests (CCTs): laboratory-based tests

The first-line clotting tests used are the activated partial thromboplastin time (APTT) and the prothrombin time (PT) normalized using the INR (International Normalized Ratio). An automated analysis of a plasmatic sample measures the time to clot formation following the addition of exogenous reagents. These tests must be interpreted with caution as they do not reflect the in vivo haemostatic response; the interaction between the vessel wall, platelets, fibrinogen and circulating coagulation factors.[1] These tests have never been validated for the prediction of haemorrhagic tendency and are performed at 37°C, normothermic values potentially overestimating haemostatic competency in hypothermic patients.

APTT tests the intrinsic and common coagulation pathways. Calcium is added to a plasma sample along with phospholipid (a platelet substitute) and kaolin. It was designed to detect deficiencies in VIII, IX and XI. It is used primarily to monitor low-dose heparin therapy, such as for interventional radiology or, vascular surgery (<5000 IU heparin).

Activated clotting time (ACT) is used to monitor high-dose heparin therapy, primarily during cardiopulmonary bypass (>20,000 IU heparin). At high heparin doses, APTT is rendered inaccurate as these values are beyond its reference range.

PT-INR tests the extrinsic and common pathways. Thromboplastin and calcium are added to citrated plasma. It was designed to detect deficiencies in II, V, VII and X. Its main clinical use has been for anticoagulant monitoring (warfarin) and detection of acquired bleeding disorders. It may also be prolonged in the presence of low plasma fibrinogen levels.

von Clauss assays measure the fibrinogen level. This remains the laboratory gold standard. The normal concentration in the blood is 1.5–4.0 g/l. However, there is wide situational variability within an individual; as an acute phase reactant it may be elevated with any form of localized or systemic inflammation. The TEG® functional fibrinogen assay (and its ROTEM™ equivalent) is an alternative method for monitoring levels. However, studies are increasingly challenging how closely this test correlates with the gold standard.[2]

Platelet count is normally between 150 and 450 $\times$ 10^9/l blood. A normal platelet count, however, does not guarantee that the circulating platelets are working. The platelet count gives no information about the platelet function.

Platelet function tests can be subdivided into platelet adherence, aggregation or activation. Bleeding time is a crude method of

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evaluation involving standardized skin incisions to evaluate vascular and platelet factors associated with haemostasis. The current gold standard is light transmission aggregometry (LTA), which measures platelet aggregation in response to an agonist. The Multiplate® is a point-of-care analyser based on impedance aggregometry. The PFA-100®, platelet function analyzer simulates primary haemostasis; blood flows through an aperture in a membrane, simulating vessel wall injury, and the time until complete occlusion (closure time) is displayed. However, it is not sufficiently sensitive to reliably detect the effect of low dose aspirin or clopidogrel.

Point-of-care tests (POCTs)

POCTs are now routine in many UK hospitals and allow the clinician access to 'real-time information', eliminating the need for empirical treatment due to long turn-around times for central laboratory testing. The cost of disposables has fallen such that they are no longer the preclusive remit of subspecialist institutions.

Thromboelastography (TEG)/thromboelastometry (ROTEM)

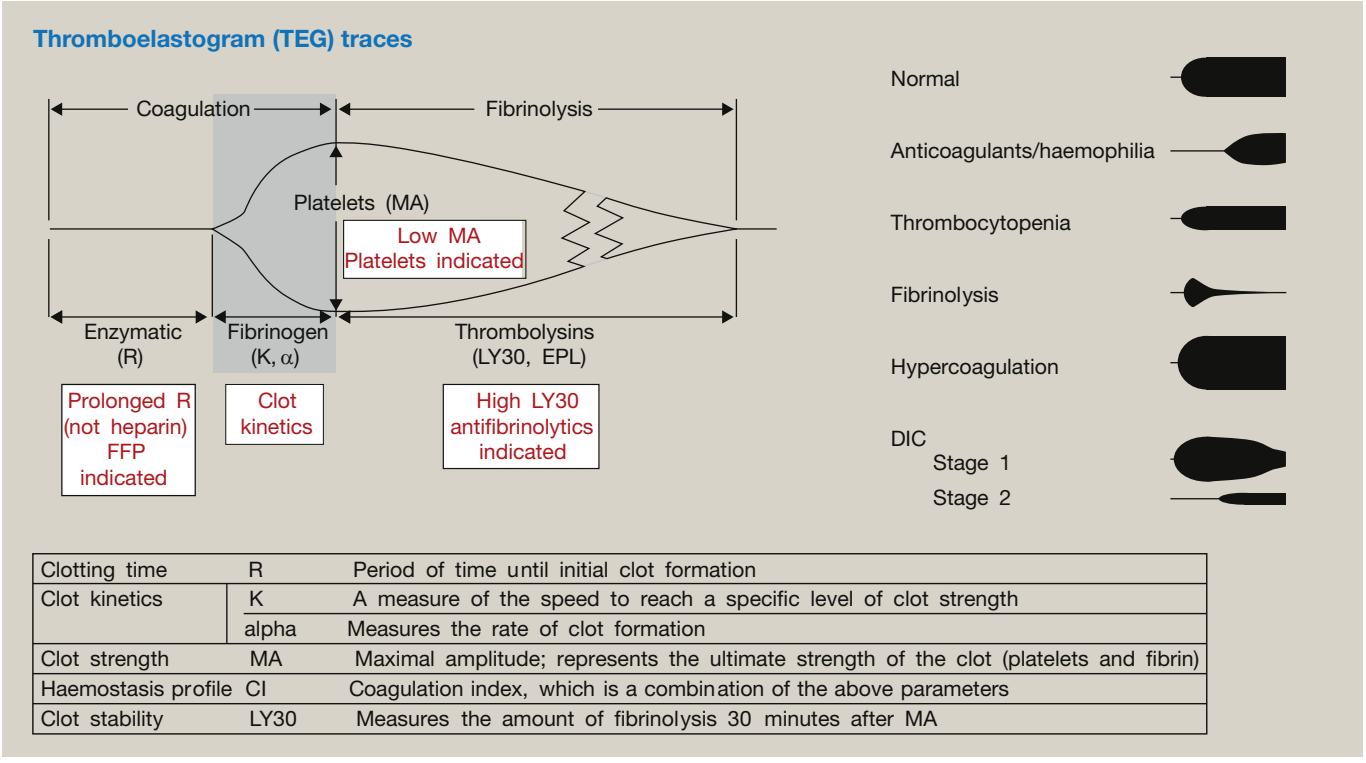
TEG/ROTEM measures the development of clot-shear elasticity in response to the formation of thrombin and platelet activation. A trace is obtained from the oscillating action of a piston in a cup containing whole blood. It provides information from the time of the first fibrin formation, reaction time (R), to the strength of the clot and fibrinolysis (Figure 1). It provides a more thorough evaluation of an individual's haemostatic state than CCTs by measuring clot strength beyond initial fibrin formation; the end point of tests such as PT-INR and APTT. As well as guiding blood component and pharmacological intervention on identification of hypocoagulable and fibrinolytic states, TEG allows recognition and subsequent thromboprophylaxis of hypercoagulable states. TEG utilizes two channels and allows endogenous/exogenous heparin effect to be identified through use of a heparinase cup. RapidTEG (rTEG) uses tissue factor as an activator in addition to kaolin to reduce the time to achieve a result. ROTEM uses heavily activated samples in four channels, which in addition allows estimation of fibrinogen level (FIBTEM) and effect of antifibrinolysis (APTEM).

Platelet mapping uses modified TEG with added reptilase and FXIIIa, to generate a whole blood-cross linked clot in the absence of thrombin generation or platelet activation. Platelet agonists are then added to heparinized whole blood producing a clot maximum amplitude (MA) which reflects degree of platelet inhibition to AA and ADP pharmacological antagonists.

Inherited coagulation disorders

Bleeding diatheses

Haemophilia A is a genetically inherited, X-linked recessive coagulation disorder and thus occurs in males (1:5000) and in homozygous females. A reduction in factor VIII results in the formation of fibrin-deficient clot. People with severe haemophilia (factor activity <1%), about 60% of the haemophilia population, present with frequent spontaneous bleeding episodes, often into the joints and muscles. Conventional coagulation tests will show a prolonged APTT with a normal PT-INR and bleeding time. Diagnostic confirmation is on identification of low (<10 IU) levels of factor VIII. Preoperative goals are to



Clotting time	R	Period of time until initial clot formation
Clot kinetics	K	A measure of the speed to reach a specific level of clot strength
	alpha	Measures the rate of clot formation
Clot strength	MA	Maximal amplitude; represents the ultimate strength of the clot (platelets and fibrin)
Haemostasis profile	CI	Coagulation index, which is a combination of the above parameters
Clot stability	LY30	Measures the amount of fibrinolysis 30 minutes after MA

Figure 1