

# Coagulation testing in the perioperative period

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## ABSTRACT

Perioperative coagulation management is a complex task that has a significant impact on the perioperative journey of patients. Anaesthesia providers play a critical role in the decision-making on transfusion and/or haemostatic therapy in the surgical setting. Various tests are available in identifying coagulation abnormalities in the perioperative period. While the rapidly available bedside haemoglobin measurements can guide the transfusion of red blood cells, blood product administration is guided by many *in vivo* and *in vitro* tests. The introduction of newer anticoagulant medications and the implementation of the modified *in vivo* coagulation cascade have given a new dimension to the field of perioperative transfusion medicine. A proper understanding of the application and interpretation of the coagulation tests is vital for a good perioperative outcome.

**Key words:** Coagulation, peri-operative, testing

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## INTRODUCTION

The coagulation process is initiated by platelets forming a plug at the location of the injury within few seconds of a breach in the vascular integrity. This constitutes the primary haemostatic mechanism.<sup>[1]</sup> Secondary haemostasis is a multifaceted interaction between plasma coagulation factors, which results in the creation of fibrin strands strengthening the platelet plug.<sup>[1]</sup> Normally, there is a balance between different factors involved in haemostasis, and mild impairment of one component can be compensated by other factors.<sup>[2]</sup> Individuals with mild coagulation impairment may never present with significant bleeding unless exposed to trauma or major surgery.<sup>[2]</sup> A detailed family history might expose a significant bleeding disorder.

Haemostasis is a combination of a number of events that occur in a sequence following the breach of vascular integrity. They include vasoconstriction, platelet aggregation, thrombus formation, recanalization and healing. Conventionally, secondary haemostasis was described as intrinsic and extrinsic pathways merging at a final common pathway.<sup>[1]</sup>

This *in vitro* model ignores the link between primary and secondary haemostasis and is not applicable *in vivo*. The currently employed cell-based model of coagulation reflects the *in vivo* process and it differs from the previous model in two key ways [Figure 1]. First, the complex formed by the tissue factor and factor VII contributes in the activation of factor IX, demonstrating that the intrinsic and extrinsic coagulation pathways are interconnected almost from the beginning of the process. Second, the complete process requires three consecutive phases: An initial phase, an amplification phase, and the propagation phase. Platelets and thrombin are actively involved in the last two phases.

A plethora of coagulation tests is available in the peri-operative period to assist the clinician in identifying coagulation abnormalities. In recent years, incorporation of various forms of coagulation monitoring has provided valuable information in the management of peri-operative coagulopathies. In this review, we discuss the coagulation tests by categorising them as pre-operative screening tests, specific laboratory tests, point of care tests including assays of platelet function.

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patients on aspirin, Uraemia and congenital impairment.<sup>[2]</sup> Platelet count is crucial in evaluating for heparin-induced thrombocytopenia on patients who are on prolonged heparin therapy. Platelet clumping and sample haemodilution are common causes for low platelet counts.<sup>[16]</sup>

### Bleeding time

Bleeding time (BT) has been widely used as a clinical test of platelet function and to predict surgical bleeding. Nonetheless, its usage in clinical practice has declined recently. It measures the overall haemostatic role of platelets and primary haemostasis *in vivo*.<sup>[2]</sup> The Simplate technique defines the duration of bleeding after a cut is made on the volar surface of the forearm with the inflated blood pressure cuff at 40 mm Hg applied around the upper arm. The normal range is 2-9 min. Numerous factors can influence the test results such as skin temperature and thickness, ethnicity, age, blotting technique, anatomic location and venous pressure.<sup>[17]</sup> There is no data supporting the use of BT in predicting excess surgical bleeding and that made its role is limited.

### Prothrombin time

The PT measures the time taken by the citrated platelet-poor plasma to form a clot in the presence of sufficient concentration of calcium and tissue thromboplastin.<sup>[2]</sup> It reflects the integrity of the extrinsic and common coagulation pathways.<sup>[16]</sup> The results can be described in one of the four ways: PT with the control value, PT expressed as international normalized ratio (INR), PT ratio, and PT index. INR was introduced to standardise the PT results across different laboratories<sup>[18,19]</sup> as thromboplastin test reagents differ in sensitivity. PT is commonly reported in seconds and expressed as the INR (normal value 0.9-1.2 s). A prolonged PT can occur in conditions such as liver disease, factor VII deficiencies, warfarin

therapy and vitamin K deficiency. Patients on warfarin therapy are routinely monitored with INR [Table 1].

### Activated partial thromboplastin time

The aPTT is the test of classic intrinsic and common pathways of haemostasis. A sample of the patient plasma is mixed with phospholipid, calcium and a contact activator (e.g. celite, kaolin, silica) and the time required for the clot formation is measured in seconds.<sup>[16]</sup> The normal range is between 25 s and 35 s. Abnormal aPTT is a reflection of most of the coagulation factor deficiencies except factor VII.<sup>[2]</sup> The factor concentrations must be reduced to roughly 30% of baseline values before the test result becomes is prolonged. The aPTT is most sensitive to factor VIII and IX deficiencies. The aPTT results are not standardised across laboratories, unlike the PT. The test is sensitive to inhibition of thrombin (unfractionated heparin). Prolonged aPTT is analysed further by mixing techniques to assess whether delayed clot formation is due to a factor deficiency or an inhibitor.<sup>[16]</sup> It is done by mixing the plasma from the patients with normal donor plasma.<sup>[16]</sup> The aPTT is prolonged in conditions such as factor deficiencies, presence of inhibitors like heparin, lupus anticoagulant, specific factor inhibitors and fibrinogen degradation products (FDPs). The aPTT is used as a screening tool for haemophilia A, haemophilia B, coagulation inhibitors and to monitor unfractionated heparin therapy<sup>[1]</sup> [Table 1].

### Thrombin time

Thrombin time (TT) tests the ability of thrombin to convert fibrinogen to fibrin in the final stage of haemostasis.<sup>[14]</sup> The normal range is 15-19 s.<sup>[2]</sup> As all the preceding reactions are bypassed, TT prolongation can occur in conditions affecting either fibrinogen or thrombin. These include hypofibrinogenemia (<100 mg/dL), dysfibrinogenemia (abnormal fibrinogen),

Table 1: Interpretation of common coagulation tests

Bleeding time	PLT count	PT	aPTT	TT	Fibrinogen	FDPs	Clinical scenario
N	N	↑	N	N	N	N	Early Vitamin K deficiency, early liver impairment, early warfarinisation, factor VII deficiency
N	N	N	↑	N	N	N	Factor deficiency-VIII, IX, XI, XII, antiphospholipid antibody, haemophilia A or B, circulating anticoagulant (heparin)
N	N	↑	↑	↑	N	N	Liver disease, hyperfibrinolysis, multiple factor deficiencies
↑	N	N	↑	N	N	N	Von Willebrand disease, PLT count may be low in some subtypes
N	↑	N	N	N	N	N	Disorders of vascular haemostasis, PLT dysfunction
↓	N/↓	N	N	N	N	N	↓production, ↑consumption (immune destruction), chemo-radiotherapy, splenomegaly
↑	↓	↑	↑	↑	↓	N	Massive transfusion, dilution effect
↑	↓	↑	↑	↑	↓	↑	Disseminated intravascular coagulation

PLT – Platelet; PT – Prothrombin time; aPTT – Activated partial thromboplastin time; TT – Thrombin time; FDPs – Fibrinogen degradation products

advanced liver disease, heparin therapy, presence of direct thrombin inhibitors, fibrinogen and FDPs.<sup>[14]</sup>

#### Reptilase time

Reptilase time is used to distinguish between the effects of heparin and FDPs when TT is prolonged. The normal range is 14-21 s.<sup>[14]</sup> Elevated TT along with the normal reptilase time indicates the presence of heparin. Elevation of both TT and reptilase time denotes low fibrinogen level or the presence of FDPs.

#### Anti-Xa assay

This assay is utilised in the monitoring of low molecular weight heparins and indirect Xa inhibitors. The patient's plasma sample is mixed with a reagent containing a certain quantity of Xa and excess antithrombin. When a chromogenic substrate of Xa is added, a colour transformation occurs in proportion to the Xa that is unbound by anti-Xa activity in the serum.<sup>[14]</sup>

#### Fibrinogen level

The normal fibrinogen values are between 160 and 350 mg/dl. It is mainly produced by the liver and levels <100 mg/dl are considered inadequate. Low levels reflect either reduced production as occurs in hereditary hypofibrinogenemia, liver impairment, severe malnutrition syndromes or due to increased consumption as in disseminated intravascular coagulation (DIC) and fibrinolysis.<sup>[2]</sup> The levels may be normal in a hypercoagulable state such as DIC as fibrinogen can markedly increase (>700 mg/dl) in response to surgery and trauma.<sup>[14]</sup> Fibrinogen consumption without DIC is an important cause of severe bleeding in patients with blood loss after major trauma.<sup>[20]</sup>

#### Fibrin degradation products and D-Dimer: Tests of fibrinolysis

The FDP assay detects the degradation products of fibrin (cross-linked or uncross-linked) and fibrinogen. The D-dimer is specific for degradation products of cross-linked fibrin. Excessive fibrinolysis results in elevated FDPs in conditions such as advanced liver disease, exogenous thrombolysis (streptokinase), fibrinolysis with CPB and DIC.<sup>[14]</sup> A rise in FDP cannot differentiate between primary and secondary fibrinolysis as it is elevated in both conditions. D-dimer reflects widespread lysis of the cross-linked fibrin of an established thrombus, such as in DIC, deep venous thrombosis and pulmonary embolism.<sup>[14]</sup>

## POINT-OF-CARE COAGULATION TESTS

Point-of-care coagulation test (POCT) also termed as near-patient coagulation test (NPT) refers to measures of coagulation that can be performed at or near the patient. These tests were introduced to overcome some of the limitations of routine laboratory based coagulation tests. They include longer turnaround time, tests are done mainly in the plasma rather than whole blood at a standard temperature of 37°C rather than the patient's temperature and providing limited information on platelet function.<sup>[21]</sup> POCTs are non-laboratory based tests with number of unique characteristics such as, to generate rapid results, need a minimal amount of whole blood, utilize less transportation, aids in blood component and haemostatic drug therapy and improve the clinical outcome. Currently, applicable devices in the perioperative settings may be categorized in four broad categories: (a) Functional assays of monitoring heparin anticoagulation, measuring the intrinsic ability of blood to form a clot (b) viscoelastic measures of coagulation (c) platelet function monitors, and (d) clotting factor tests.

## FUNCTIONAL ASSAYS OF MONITORING HEPARIN ANTICOAGULATION

#### Activated clotting time

The ACT is extensively used to monitor systemic heparin therapy as in cardiac surgery, haemo-filtration, extracorporeal oxygenation and cardiac catheterisation. Hattersley first described the use of Hemochron ACT in 1966.<sup>[1]</sup> The accepted normal range is 90-150 s. The test utilises the activation of coagulation through the intrinsic pathway when fresh whole blood is incubated with kaolin at 37°C.<sup>[22]</sup> The result will be influenced by the time at which the "baseline" measurement is done.<sup>[23]</sup> The baseline ACT may decrease after surgical incision. In the absence of aprotinin administration, ACT values around 480s are considered safe in the context of CPB, whereas values around 700 s are needed in the presence of systemic aprotinin.<sup>[1]</sup> Some of the ACT devices commercially available are Hemochron®, Hepcon® and ACT II®, Hemochron Jr. signature® and the newer electrochemically based ISTAT.

Activated clotting time testing is a popular test due to its low cost, simplicity, and linear response at high heparin concentration.<sup>[16]</sup> Lack of sensitivity at low heparin concentration, poor reproducibility and false prolongation of values with hypothermia, coagulation factor deficiencies, group IIb/IIIa inhibitors, warfarin,

platelet function abnormalities, lupus antibodies and haemo dilutions are some of the limitations of ACT monitoring.<sup>[16,23,22]</sup>

### High-dose thrombin time

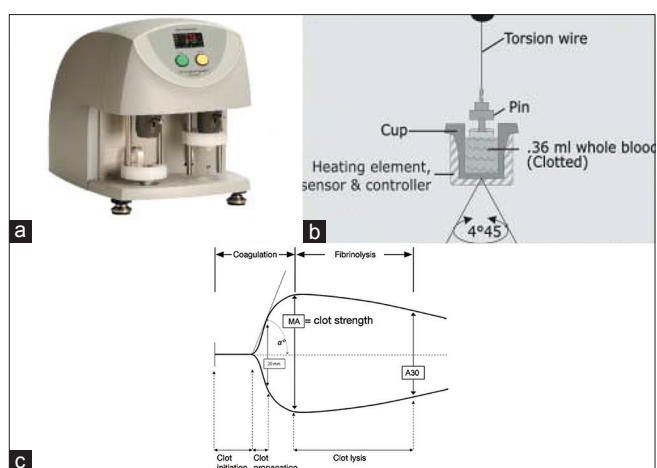
The high-dose thrombin time is another functional assay of systemic heparin anticoagulation utilised in cardiac surgery. A prolongation will correlate with the anticoagulant effect of heparin.<sup>[16]</sup>

## VISCOELASTIC MEASURES OF COAGULATION

Originally developed in the 1940s, viscoelastic measures of coagulation have drawn big attention over the last few years, and many innovative viscoelastic monitors are available today. These monitors are unique in measuring the whole spectrum of clot formation starting from the early fibrin strand generation till clot retraction and fibrinolysis.<sup>[16]</sup> The coagulation is assessed in real time on whole blood that permits *in vivo* coagulation interaction with red blood cells and platelets and provides critical information on platelet function.<sup>[21]</sup> The substantial difference between the *in vitro* and *in vivo* coagulation assessment is that viscoelastic assessments measure the coagulation under static conditions without any flow in a cuvette outside the vasculature. Hence, results based on the viscoelastic properties have to be interpreted with caution by correlating with the clinical conditions.<sup>[21]</sup> Thromboelastograph (TEG<sup>®</sup>), rotation thromboelastography (ROTEM<sup>®</sup>) and Sonoclot<sup>®</sup> are some of the devices with proven utility in cardiac surgery, trauma, hepatobiliary surgery and obstetrics.<sup>[15]</sup>

### Thromboelastograph

The TEG<sup>®</sup> was developed by Hartert in 1948. The TEG<sup>®</sup> analyses and graphically displays the changes in viscoelasticity across all stages of clot formation and resolution. This is in contrast to many other coagulation tests where the time to first fibrin formation is used as an end point.<sup>[1]</sup> The TEG is a fibrinolysis sensitive assay that analyses the interaction between platelets, fibrinogen and clotting factors and aids in the diagnosis of hyperfibrinolysis in the context of bleeding.<sup>[21]</sup> The device uses a tiny 0.35 ml of blood loaded into two disposable heated cups (37°C) containing contact activators. A pin is suspended in the blood sample by a torsion wire attached to an electronic recorder, and the cup rotates through 4°45' in each direction lasting 10 s<sup>[22]</sup> [Figure 2]. With the formation of the clot, the pin gets embroiled within the clot and the torque of the cup is transmitted across the pin and the torsion wire to



**Figure 2:** Working principle of TEG<sup>®</sup>, the equipment (a), the graphical representation of working principle with components (b), the final TEG<sup>®</sup> signal tracing (c)

a mechano-electrical transducer [Figures 2 and 3]. The generated electric signal gets converted into a cigar shaped graphical display demonstrating the characteristic of shear elasticity against time.<sup>[21]</sup> The shape of the graphical display aids in a quick qualitative assessment of different coagulation states (hypo, normal, hyper) representing specific abnormalities in clot formation and fibrinolysis.

### Rotation thromboelastography

The ROTEM<sup>®</sup> device uses a modification of the TEG<sup>®</sup> technology using 0.30 ml of blood. The TEG<sup>®</sup> uses kaolin as the contact activator whereas the ROTEM<sup>®</sup> incorporates tissue factor in the EXTEM<sup>®</sup> cuvette (clot formation and fibrinolysis, extrinsic pathway) and contact activator in the INTEM<sup>®</sup> cuvette (intrinsic pathway)<sup>[22]</sup> [Figure 4]. Both devices permit coagulation monitoring under systemic heparinisation as in CPB, as they have heparinase containing cuvettes. This enables removal of the heparin effects on the tracing and helps identifying residual effects of heparin, as well as heparin rebound after protamine reversal.<sup>[22]</sup>

The tracings for both TEG<sup>®</sup> and ROTEM<sup>®</sup> are similar [Figure 3]. However, it is important to note that the terminologies and reference ranges are unique for each device. The various parameters derived from these devices and their interpretations are depicted in Table 2. Both TEG<sup>®</sup> and ROTEM<sup>®</sup> allow the assessment of fibrinogen function using tests such as the Functional fibrinogen and FIBTEM<sup>®</sup>.<sup>[24]</sup>

### Sonoclot analyser<sup>®</sup>

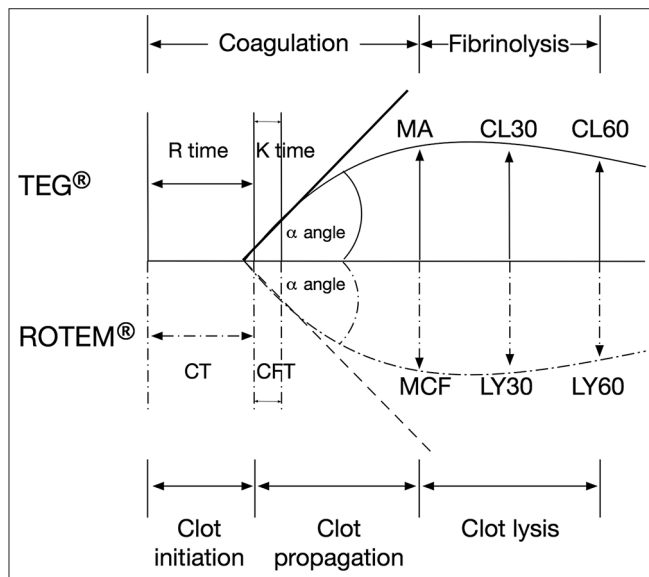
In this device, a brisk vertically vibrating probe is inserted into a 0.4 ml blood sample [Figure 4]. The

development of the clot creates an impedance to probe movement and creates an electrical signal and characteristic “signature”.<sup>[21]</sup>

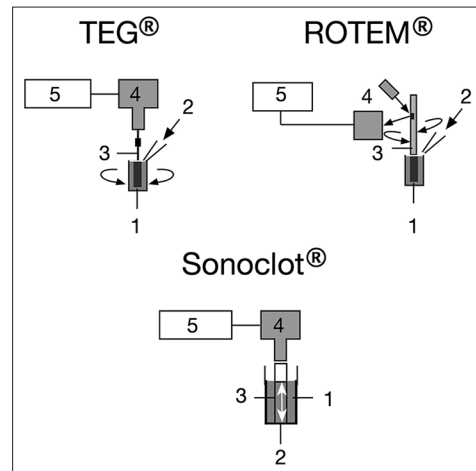
**PLATELET FUNCTION MONITORING**

Platelet disorders can occur due to various congenital and acquired defects affecting the surface receptors participating in aggregation or adhesion, storage granules or other mechanisms.<sup>[25]</sup> Quantitative and qualitative platelet dysfunction, as well as antiplatelet drugs, can impact primary haemostasis. Both

qualitative assessments of platelet dysfunction (optical aggregometry) and quantitative assessment of platelet activation (flow cytometry) are possible through standard laboratory-based testing methods. Although these tests represent standards of care, they are technically challenging, time-consuming and expensive.<sup>[16]</sup> Numerous POCT devices are available to aid the clinician to monitor the platelet function in an attempt to ascertain their effectiveness of antiplatelet drugs and to confirm recovery of function when they are ceased.<sup>[26]</sup> Many POCT platelet function monitors have been created with specific activators to detect P2Y12 antagonists such as thienopyridines (clopidogrel, prasugrel) cyclooxygenase inhibitors (aspirin) and glycoprotein IIb/IIIa antagonists (abciximab,



**Figure 3:** Comparative tracing of a normal TEG® and ROTEM®. The bold line represents TEG® and corresponding ROTEM® tracing is represented by dotted line. R, reaction time; α angle, slope between R and K for TEG® and slope of the tangent at 2 mm amplitude for ROTEM®; MA, maximum amplitude; CL 30, clot lysis at 30 min; CL 60, clot lysis at 60 min; CT, clotting time; CFT, clot formation time; MCF, maximum clot firmness; LY30, lysis at 30 min; LY60, lysis at 60 min



**Figure 4:** Bio-mechanical working principles behind the three viscoelastic coagulation monitoring devices: (1) blood sample in rotating cup for TEG® and in cuvette for ROTEM® and Sonoclot®, (2) coagulation activator, (3) pin and torsion wire for TEG®, pin and rotating axis for ROTEM® and disposable plastic probe for Sonoclot®, (4) electromechanical signal transducer/signal detector (5) data processor

**Table 2: Interpretation of TEG® and ROTEM® parameters**

TEG®	ROTEM®	Definition	Significance
R (reaction time): WB 4-8 min	CT INTEM 137-246s EXTEM 42-74s	Time until initiation of fibrin formation, taken as a period to 2 mm amplitude on the tracing	Concentration of soluble clotting factors in the plasma
K time: WB 1-4 min	CFT INTEM 40-100s EXTEM 46-148s	Time period for the amplitude of the tracing to increase from 2 to 20 mm	Indicates clot kinetics
α angle: WB 47-74°	α angle INTEM 71-82° EXTEM 63-81°	Angle between the tangent to the tracing at 2 mm amplitude and the horizontal midline	Rapidity of fibrin build up and cross-linking
MA: WB 55-73 min	MCF INTEM 52-72 mm EXTEM 49-71 mm	Greatest vertical width achieved by the tracing reflecting maximum clot strength	Number and function of PLTs and fibrinogen concentration
CL30	LY30	Percent reduction in amplitude 30 min after MA	Clot stability and fibrinolysis
CL60	LY60	Percent reduction of clot firmness 1 h after MCF	Clot stability and fibrinolysis

CFT – Clot formation time; CT – Clotting time; MCF – Maximum clot firmness; MA – Maximum amplitude. Normal ranges given in italics. TEG® WB – Whole blood, ROTEM® – INTEM contact activator and EXTEM tissue factor. (Reproduced from Amit Srivastava, Andrea Kelleher, Point-of-care coagulation testing, Contin Educ Anaesth Crit Care Pain (2013) 13 (1): 12-16. by permission of Oxford University Press)

tirofiban). The utility of commonly available POC platelet monitoring devices in assessing the effects of antiplatelet medication is depicted in Table 3.<sup>[26]</sup> It has to be noted that platelet function monitors from different manufacturers assay differing aspects of platelet-or plasma-mediated haemostasis. A brief description of the platelet function analyser-100 (PFA-100) is given below.

#### Platelet function analyser-100

The PFA-100 is unique between both POC and laboratory-based platelet function monitors by incorporating high-shear conditions to stimulate small vessel injury and measures platelet adhesion and aggregation.<sup>[27]</sup> The device is effective in detecting aspirin mediated platelet dysfunction as well as von Willebrand's disease. Further, this system allows to test for P2Y mediated blockade (clopidogrel, P2Y12) using the new INNOVANCE® PFA P2Y cartridge.<sup>[28]</sup> Haemodilution and interference by thrombocytopenia are some of the limitations of PFA-100.

#### NEAR PATIENT CLOTTING FACTOR TESTS

Point-of-care coagulation tests are also available for the evaluation of PT, aPTT, INR. These tests are widely used in the hospital and the community setting to monitor patients who are on warfarin therapy. It is a common practice to bed side INR test in surgical patients on warfarin therapy.

#### CHOOSING THE CORRECT POINT-OF-CARE COAGULATION TEST DEVICE

The selection of POCT devices should be tailored to the clinical situation. While detection and management of hyperfibrinolysis and plasma coagulation disorders are important aspects during liver transplant and trauma, heparin effects, disorders of primary haemostasis such as thrombocytopenia and acquired platelet dysfunction are paramount in cardiac surgery. Conversely, platelet aggregation inhibitors are vital in

cardiology especially in the context of drug-eluting stents.<sup>[29]</sup>

#### LIMITATIONS OF POINT-OF-CARE COAGULATION TEST DEVICE

Point-of-care coagulation test results may not necessarily mirror those values from laboratory-based testing. Techniques based on whole blood are likely to be different from laboratory measurements in conditions such as haemodilution and platelet dysfunction (e.g. CPB). The reliability of these tests depends on the experience of the operator and appropriate calibration.<sup>[1]</sup> Reagent sensitivity differs between manufacturers and even between two sets of reagents. These tests are expensive, needing robust systems in place for quality control, and ongoing staff education. A thorough familiarity of the devices' functioning, methodology and strengths and weakness is imperative.

#### COAGULATION TESTS IN THE PRESENCE OF NEWER ANTICOAGULATION AGENTS

The introduction of novel anticoagulant agents such as dabigatran, rivaroxaban, apixaban, argatroban and fondaparinux had further complicated the interpretation of coagulation tests. A detailed description of the effects of these agents on perioperative coagulation tests is beyond the scope of this review. It is worth reiterating that though these agents may influence routine tests such as the PT, aPTT and TT, they are not suitable to measure the effect of these medications and that normal routine tests do not exclude an effect of them on the preoperative haemostasis.

#### SUMMARY

A plethora of coagulation tests is available to the anaesthesiologists to guide patient management in the perioperative period. There is no role for routine preoperative coagulation screening in otherwise normal patients. When ordering these tests, a focused history along with co-morbidities and antithrombotic medications that could impact the haemostatic mechanisms have to be considered. Whenever abnormal haemostasis is encountered, both screening and specific tests would help in establishing whether the impairment is due to defective thrombin generation and clot formation or due to platelet dysfunction. Innovations in POCT can guide the clinician in transfusion management and haemostatic therapy

**Table 3: Role of point-of-care platelet function testing devices in assessing the effects of antiplatelet medications**

Device	Antiplatelet medications
PFA-100®	Aspirin
Plateletworks	Aspirin, P2Y12 antagonists, GpIIb/IIIa antagonists
TEG platelet mapping	Aspirin, P2Y12 antagonists, GpIIb/IIIa antagonists
VerifyNow	Aspirin, P2Y12 antagonists, GpIIb/IIIa antagonists
MultiPlate	Aspirin, P2Y12 antagonists, GpIIb/IIIa antagonists

PFA – Platelet function analyser

during surgery. If applied in a proper way, near patient tests of coagulation can simplify the rational use of blood products and reduce inappropriate transfusion and related morbidity.

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