18 Intraoperative Coagulation Monitoring in Liver Transplant Surgery

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Abbreviations

ACT	Activated clotting time
DIC	Disseminated intravascular coagulation
DVT	Deep-vein thrombosis
ECMO	Extra-corporeal membrane oxygenation
ESLD	End-stage liver disease
FDPs	Fibrinogen degradation products
PAI-1	Plasminogen activator inhibitor-1
POC	Point-of-care
ROTEM	Rotational thromboelastometry
TEG	Thromboelastography
t-PA	Tissue plasminogen activator

18.1 Introduction

Coagulation occurs in three phases such as primary haemostasis, coagulation and fibrinolysis, and liver dysfunction affects all three functions [1]. The liver is responsible for the synthesis of all clotting factors (except von Willebrand factor—vWf), all anticoagulants, as well as production of fibrinolytic proteins [2], and therefore haemostasis abnormality in liver disease is multifactorial—Box 18.1.

Box 18.1 Haemostatic abnormalities in liver disease are due to [2]

- Thrombocytopenia and qualitative dysfunction
  - Hypersplenism contributing to sequestration of platelets
  - Decreased thrombopoietin production
  - Immune-mediated platelet destruction
  - Renal impairment and uraemia accompanying liver failure [3]
- Impaired humoral coagulation
  - Inadequate coagulation factor production
  - Increased coagulation factor consumption
  - Vitamin K deficiency (due to which abnormal clotting factors are produced as there is lack of gamma carboxylation)
- Excessive fibrinolysis
- Disseminated intravascular coagulation

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The historical assumption that haemostasis in liver disease depicts a bleeding tendency is now replaced with the concept of a 'rebalanced' haemostasis between procoagulant, anticoagulant and fibrinolytic system due to a parallel deficiency of requisite factors. The tendency towards bleeding or thrombosis will depend on the circumstantial risk factors such as volume status, infections, alcohol, medications and renal function [4, 5]. Coagulopathy is also an essential component of acute liver failure, the other component being hepatic encephalopathy. Plasma concentration of coagulation factors is drastically reduced due to high cytokine concentration. High levels of acute phase reactant PAI-1 (plasminogen activator inhibitor-1) found in acute liver failure predispose these patients towards hypofibrinolysis [1].

Liver transplantation is the only treatment which can restore normal haemostasis in patients with end-stage liver disease or acute liver failure. It is an intricate procedure during which coagulopathy may precipitate into a catastrophe at a dramatic pace, hence requiring rapid diagnosis and management. The complex nature of haemorrhage increases the likelihood of a therapeutic misadventure, if a targeted approach is not followed [6]. Transfusion is associated with increased morbidity and mortality and may contribute to the alloantibody load and increase the risk of allograft rejection [3]. Moreover, an adverse association of red cell (RBC) transfusion on survival rates following liver transplant has been demonstrated; therefore, there is a constant endeavour to reduce transfusion [7]. Advancements in modalities for diagnosing and managing coagulopathy have been a major contributing factor in improving the 5-year survival rate from 72% in 1998 to 90% in 2010 in the United States [3].

Transfusion and coagulation management algorithms based on the point-of-care tests can be useful adjuncts to reduce transfusion requirement and thereby affect morbidity and mortality.

18.2 Intraoperative Changes in Each Phase

Management of coagulopathy in patients undergoing liver transplant poses a unique challenge due to the low haemostatic reserve in these patients, prolonged duration of surgery and phase-specific requirements during each phase of the procedure, described as below [Table 18.1]:

Table 18.1 Summary of coagulation abnormalities—phase wise

Dissection	Surgical bleeding, slight worsening of coagulopathy
Anhepatic	Loss of coagulation factors, fibrinolysis
Reperfusion/ neohepatic	Initially—hyperfibrinolysis, entrapment of platelet and release of heparin
	Followed by resolution of hyperfibrinolysis

18.2.1 Dissection Phase

This phase involves dissection of adhesions, transection of collaterals and manipulation of major structures to facilitate mobilization of the liver, contributing to major blood loss. There is a slight deterioration of the pre-existing coagulopathy due to surgical stress; however, surgical bleeding is the hallmark of this phase.

Aetiology of the liver disease is also a factor which influences intraoperative requirement of blood products in this phase. For example, patients with hepatocellular carcinoma are usually hyper-coagulopathic. Similarly, patients with primary biliary cirrhosis and primary sclerosing cholangitis are likely to have a hypercoagulopathic state with reduced fibrinolytic activity [8]. Enhanced fibrinolysis contributes to blood loss in only 10–20% of the cases [1].

18.2.2 Anhepatic Phase

This phase extends from occlusion of the hepatic vasculature till reperfusion of the new liver into the recipient's circulation. Major vessels have already been clamped during the dissection phase which limits the surgical bleed. However, since the liver is out of circulation, the characteristic feature of this phase is loss of synthesis and clearance of coagulation factors.

There is an increased level of t-PA (tissue plasminogen activator), due to release from endo-

thelial cells and decreased clearance in absence of the liver, which contributes to hyperfibrinolysis seen in this phase [1]. This later continues into the reperfusion phase [9].

18.2.3 Post-reperfusion/Neohepatic Phase

This phase begins with the reperfusion of the new liver into the recipient's circulation often resulting in uncontrollable bleeding during the first few minutes, thus warranting immediate management and control [1].

During the reperfusion of the new liver, further t-PA from the endothelium of the replaced organ is released and hyperfibrinolysis is at its peak [9]. This period is further characterized by abnormalities related to thrombocytopenia and heparin-like effect of donor liver. There is a gradient of platelet count of up to 50% between the arterial and venous circulation representing the profound entrapment of platelets in the donor sinusoids. The ischemic donor liver endothelium releases heparinoids, which adds to the heparin load following heparinization of donor liver prior to harvesting [10]. This initial hyperfibrinolysis gradually resolves with clearance of t-PA and increased production of PAI-1.

18.3 Monitoring Coagulation During Liver Transplant Surgery

Bleeding during liver transplantation, as mentioned above, occurs due to several reasons [8]:

- Surgical factors—previous abdominal surgery, portal hypertension, portal vein thrombosis
- Donor-related factors—length of ICU stay, duration of cold ischaemia time
- Recipient-related factors—severity of disease, age, renal dysfunction and comorbidities
- Factors arising from operative milieu—acid-base balance, hypocalcaemia, hypothermia
- Inherent coagulopathy of the patient

Due to disparity between the increasing demand for organs and limited supply of donors, there is an increasing trend of marginal and high-risk donors being accepted. The recipients who receive organs from these donors are at an increased risk of perioperative coagulopathy resulting from delayed graft function or slow-graft function commonly seen with these donor grafts [3].

Coagulation monitoring and management for major surgical procedures is challenging and is usually based on standard laboratory tests. However, these tests, in the setting of ESLD (end-stage liver disease), are less reliable especially in the background of bleeding during liver transplant, where diagnosis has to be precise and treatment prompt. The standard laboratory tests are briefly described.

18.3.1 Standard Laboratory Tests

The clotting process can be divided into four phases [11] (Fig. 18.1):

- Primary haemostasis
- Thrombin generation
- Clot formation
- Clot breakdown/lysis

Conventional or standard laboratory tests at best reflect the thrombin generation phase.

These tests include:

- Prothrombin time (PT)
- Activated partial thromboplastin time (aPTT)
- Platelet count
- Fibrinogen levels

18.3.2 Prothrombin Time (PT)

Also called tissue factor-induced coagulation time, the prothrombin time test was developed in 1935 to titrate coumarin doses [12]. It is sensitive to factors I, II, V, VII and X and is performed by incubating plasma at 37° with tissue thromboplastin (tissue factor plus phospholipid) and cal-

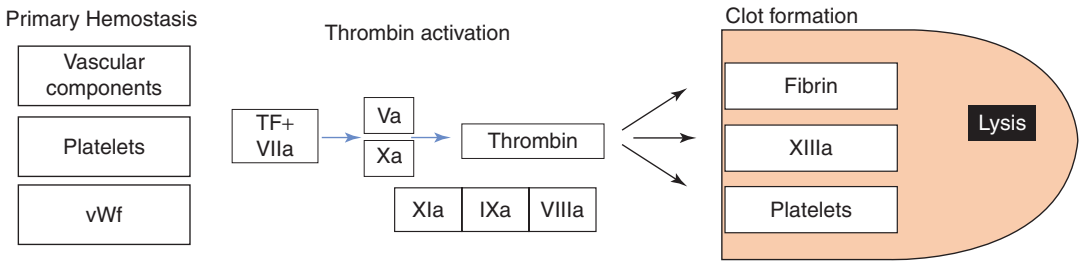


Fig. 18.1 This is the arbitrary subdivision of the coagulation system which is an interaction between vascular, cellular and humoral components

cium at standard pH. It detects the time needed for platelet-poor plasma to clot and reflects the integrity of the extrinsic and common coagulation pathway [13]. Detection of fibrin strands using either a photo-optical or electromechanical device is the end point of the test [10]. It is reported in seconds and normal value is 0.9–0.12 s [13].

18.3.3 International Normalized Ratio (INR)

Standardization is based on the responsiveness to a singular type of thromboplastin which is then measured by International Sensitivity Index and converted to the INR (international normalized ratio) value mainly to account for inter-device variations in PT measurements. INR was introduced in 1983 to harmonize results of PT across laboratories. It is defined as (patient PT/control PT)^{ISI} [12, 14].

18.3.4 Activated Partial Thromboplastin Time (aPTT)

It was developed in 1953 and then modified in 1961. It is performed to monitor heparin therapy during thrombolysis. This test is sensitive to coagulation factors I, II, V, VIII, IX, XI and XII, heparin, fibrinogen degradation products, hypothermia and hypofibrinogenaemia. The term 'partial thromboplastin' indicates that the reagent contains phospholipids (as a substitute for the platelet membrane) but no tissue factor, distinguishing it from the PT [10]. Platelet-poor plasma is incubated with partial thromboplastins, calcium and an activator (e.g. celite, kaolin, silica) at 37° and standard pH [13]. It reflects the integrity of the intrinsic and common coagulation pathway and the normal range is between 25 and 35 s [13]. Factor deficiency must be reduced to almost 30% before the test is able to demonstrate abnormality.

18.3.5 Thrombin Time [13]

The ability of thrombin to convert fibrinogen to fibrin (fibrin polymerization) in the final stage of haemostasis is measured with this test. A standard concentration of human thrombin is added to citrated, platelet-poor plasma and time to clot formation is measured. Clot formation requires the presence of fibrinogen and the absence of thrombin inhibitors [10]. Its normal value is 15–19 s. It helps in establishing conditions such as hypofibrinogenaemia, dysfibrinogenaemia, presence of direct thrombin inhibitors, fibrinogen and FDPs (fibrinogen degradation products) since it bypasses all the preceding reactions before the conversion of fibrinogen. It is also used to monitor fibrinolytic therapy and to detect heparin resistance.

18.3.6 Platelet Count

Platelet count is routinely measured by automated machines [6]. Formation of a satisfactory platelet plug may be impaired if the platelet

count is low, if platelets are functionally inert or if the patient is on antiplatelet drugs. However, the platelet count reflects the quantity of platelets in numbers and does not provide information regarding their function [13]. The normal range is between 150,000 and 440,000 cu mm and counts less than 150,000 cu mm reflect thrombocytopenia. Platelet clumping and sample haemodilution are common causes for low platelet count. Platelet count plays an important role in demonstration of HITS (heparin-induced thrombocytopenia).

18.3.7 Fibrinogen

Measures the amount of fibrinogen in the system. The two most frequently used tests in routine clinical practice are the Clauss assay and the PT-derived fibrinogen level. Fibrinogen values range between 160 and 350 mg/dL [13]. Reduced levels may be due to impaired production (such as liver disease) or increased consumption (such as disseminated intravascular coagulation (DIC) and fibrinolysis). Fibrinogen levels may also be falsely elevated in the presence of synthetic colloids such as hydroxyethyl starch often used for fluid resuscitation [6].

18.3.8 Fibrinogen Degradation Products (FDPs) and D-Dimer (Tests of Fibrinolysis)

This assay detects degeneration products of fibrin (either cross-linked or uncross-linked). The D-Dimer is specific for degraded products of cross-linked fibrin. These may be elevated in advanced liver disease, exogenous thrombolysis and fibrinolysis following cardiopulmonary bypass and DIC. Elevated levels cannot differentiate primary and secondary fibrinolysis. Elevated D-dimer is non specific and is the result widespread lysis of cross-linked fibrin of established thrombi, as seen in deep-vein thrombosis (DVT) and pulmonary embolism.

18.3.9 Limitations of Conventional Tests

Though commonly done in cirrhotic patients, these tests do not reflect the exact picture of coagulation. The levels of naturally occurring anticoagulants as protein C and antithrombin are also reduced as are procoagulants and the full anticoagulant activity cannot be expressed. These tests have a direct relationship to the degree of decompensation in cirrhosis and may be useful in predicting prognosis but not for predicting bleeding or thrombosis in these patients [15]. The coagulation system in these patients seems to be more 'balanced' than suggested by traditional tests. PT and aPTT can assess the speed of fibrin strand formation; they do not assess the mechanical and functional properties of the clot over time. INR monitoring will at best be an indicator of synthetic function rather than to assess the actual probabilty to bleed [16, 17]. The current concepts in coagulation advocate the cell-based model which emphasizes on the interaction between platelets, vascular endothelium and fibrinolytic factors in the haemostatic mechanism. Standard laboratory tests which are performed in plasma do not demonstrate these interactions and therefore cannot guide therapy [8, 18].

Fibrinogen levels coupled with platelet count would be more meaningful than INR as a measure of risk of bleeding and target values have been ascertained as 120–150 mg/dL; however, these values are with reference to trauma settings [4]. Platelets contribute to thrombin formation and therefore a theoretical possibility of reduced thrombin generation exists in cirrhosis. However, this has not been clinically demonstrated in stable cirrhotic patients with platelet count $>60 \times 10^9$. Under physiological condition of flow, platelets from these patients are able to interact normally with collagen and fibrinogen. Platelet count is purely quantitative and cannot detect platelet dysfunction. A school of thought suggests the thrombin generation test is likely to provide a better clinical picture in cirrhotic patients for the prediction of bleeding or guided decision making [12].

None of the conventional coagulation tests detect or identify the fibrinolytic process; they can only detect products of degeneration which is highly non-specific [16]. Coagulation results can be affected adversely by poor sampling technique such as underfilling the tube may prolong clotting times artefactually due to over-anticoagulation. Reduced haematocrit may reduce plasma volume and prolong clotting times in the sample [10].

18.4 Point-of-Care Coagulation Testing

Preoperative treatment of infection, optimization of renal status, surgical management of active bleeding, striving to preserve normothermia, maintaining low central venous pressure, normocalcaemia and pH levels within physiological limits during the intraoperative period contribute towards reducing bleeding during liver transplant surgery. However, despite all these measures, the delicate surgical milieu may be disrupted due to the inherent coagulation imbalances resulting in a 'dynamic haemostatic profile' [19].

Apart from a longer turnaround time, standard laboratory tests may fail to predict the risk of bleeding as they are not affected by profibrinolytic susceptibility, anticoagulant protein C, antithrombin and tissue factor pathway inhibitor, and endothelium-derived haemostatic process thus making them unsuitable for managing coagulation during liver transplant surgery. The risk of thrombotic events in these patients is substantial and mortality associated with these events is manifold. These events can be prevented by judicious administration or avoiding inadvertent transfusions of products [17]. This is where intraoperative point-of-care coagulation monitoring can aid in ensuring transfusion of blood products in a targeted manner, thus preventing unwarranted transfusion and its deleterious effect. Therefore, point-of-care devices provide immediate, accurate, real-time and comprehensive picture of the patient's coagulation status (Box 18.2).

Box 18.2 Advantages of point of care testing [20]

- Small volume of blood is needed (<1 to 5 mL).
- Rapid availability of results; therefore decisions can be made faster.
- Transporting time is saved.
- Pre-analytical steps (centrifuging, etc.) can be avoided.
- Persons without training in medical technology may perform the test.
- Tests are easy to learn.

A point-of-care test is defined as a rapid bedside diagnostic test to aid the clinician in directing therapeutic intervention. The aim of perioperative coagulation testing is the detection of deranged haemostasis and to initiate treatment rapidly; therefore point-of-care tests would be the way forward to improve clinical efficiency. Applicable devices in the perioperative setting are classified into four broad categories [13]:

(a) Functional assay of monitoring heparin anticoagulation
(b) Platelet function monitors
(c) Near-patient clotting factor tests
(d) Viscoelastic measures of coagulation

Despite the fact that some of the classical criteria for designation of a test to be point-of-care test (includes easy measurement, easy interpretation and no handling of reagent) may not be met by some of these tests, they have still been classified as point-of-care coagulation tests [20].

18.4.1 Functional Assay of Monitoring Heparin Anticoagulation [13]

18.4.1.1 Activated Clotting Time (ACT)

This test is widely used to monitor systemic heparin therapy in cardiac surgery, haemo-filtration,

ECMO (extra-corporeal membrane oxygenation) therapy, cardiac catheterization and interventional radiology [20].

First described in 1966, it utilizes the activation of coagulation through the intrinsic pathway when fresh whole blood is incubated with glass beads, kaolin or celite at 37°. Two millilitres of whole blood is added to a test tube containing celite and a ferro-magnetic bar. The tube is gently rotated within the test well. As coagulation occurs, the bar also begins to rotate with the tube and the rotation is detected by a magnetic sensor. The time to formation is recorded by a timer; the normal value is 90–150 s. ACT is a popular test due to its low cost, simplicity and linear response at high heparin concentration [10]. The test is not sensitive at low heparin concentrations, hypothermia, coagulation factor deficiency, IIb/IIIa inhibitors, warfarin therapy, lupus antibodies and haemodilution.

There is a variant of ACT called heparin management test (HMT) which is capable of measuring prothrombin time and activated partial thromboplastin time [21].

18.4.2 Platelet Function Monitoring

Factors such as congenital and acquired defects affecting the surface receptors participating in aggregation or adhesion, storage granules or other mechanisms can contribute to platelet dysfunction. Point-of-care platelet function monitors are now available to aid the clinician to monitor platelet function. Some monitors have specific activators to detect P2Y12 antagonists such as thienopyridines (clopidogrel, prasugrel), cyclooxygenase inhibitors (aspirin) and glycoprotein IIb/IIIa antagonists (abciximab, tirofiban).

18.4.2.1 Platelet Function Analyser-100

The PFA-100 monitors measure platelet adhesion and aggregation by incorporating high-shear conditions to stimulate small vessel injury. A total of 800 µL of citrated whole blood is drawn through a 150 µm hole in a collagen-coated membrane bonded with either epinephrine or ADP. The shear stress of whole blood being drawn through a vacuum leads to platelet activation and promotes platelet adherence and aggregation and proceeds to form a primary plug which seals the hole [21]. This is sensed by a pressure transducer and usually occurs in 81–166 s with epinephrine and 54–109 s with ADP [10].

The response to epinephrine detects aspirin-induced platelet dysfunction. Both channels detect dysfunction in patients with von Willebrand's disease and uraemia [21].

The drawback is the analysis has to be performed 30–120 min after venepuncture. Haemodilution and interference by thrombocytopenia are some of the limitations.

18.4.3 Near-Patient Clotting Factor Test

Point-of-care coagulation tests are also available for the evaluation of PT, aPTT and INR.

Hemochron Jr. signature is a hand-held device used to derive ACT, aAPTT and PT. Test-specific cuvettes are pre-warmed to 37 °C, onto which 50 µL of fresh or citrated whole blood is placed and then mixed with the test-specific reagent. As coagulation occurs, optical sensors detect the impeded movement.

CoaguChek is another near-patient test that uses reflectance photometry to derive INR.

These point-of-care tests (of PT and APTT) can be affected to a variable extent in patients with liver disease, septicaemia, trauma, etc. Hence, these point-of-care tests for PT and APTT are approved only for monitoring anticoagulation therapy and their value in other clinical situations is limited.

18.4.4 Viscoelastic Measures of Coagulation

Standard laboratory tests (other than platelet count), being plasma-based tests, only reflect the initial stages of the coagulation. Viscoelastic, point-of-care coagulation tests use whole blood

and can provide insight into all components such as coagulation initiation to fibrinolysis, the strength and stability of the clot.

The point-of-care viscoelastic tests validated for liver transplant include:

1. Thromboelastography (TEG)
2. Rotational thromboelastometry (ROTEM)
3. Sonoclot

18.4.4.1 TEG/ROTEM: Introduction

Invented in 1948 by Hartert, they assess the viscoelastic properties of whole blood under low shear conditions and provide valuable information about all stages of haemostasis until resolution of the clot [22]. Use in liver transplant was first described in 1985 by Kang et al. and later in cardiac surgery in 1995 [9].

In contrast to many other coagulation tests where the time to first fibrin formation is used as an end point [13], these tests are based on the clinical principle that

- The end result of haemostasis is formation of clot and
- The physical properties of this clot (rate of formation, strength and stability) are a reflection of the patients' in vivo haemostasis status [22, 23].

Specific activators have been used to improve standardization and practicability [11]. Formation of the clot is a result of interaction between the cellular components of blood and coagulation proteins. The interaction between fibrinogen, platelets and clotting factors are therefore assessed with a single test [10]. The physical properties of the clot are measured and translated into electrical signals which are used to create graphic and numerical output which are interpreted in terms of hypocoagulable, normal or hypercoagulable state, with or without lysis.

Of course, the importance of periodic assessment of surgical field and communication with surgical teams cannot be underestimated. Surgical attempts to control visible source of bleeding, temperature monitoring, acid base and electrolyte monitoring contribute to monitoring coagulopathy during the transplant procedure [6].

18.4.4.2 Thromboelastography (TEG)

The term thromboelastograph is used to describe the trace produced during the test. The term thromboelastography and TEG have been used to describe the technique (Fig. 18.2). In 1996, TEG® became the registered trademark of the Haemoscope Corporation [9].

TEG gives a graphic representation of clot formation and subsequent lysis; 340-360 μL of whole blood sampled from the patient is incubated in a heated cup at 37°. Care should be taken not to underfill the cups as this will result in prolongation of the coagulation time. A pin connected to a detector system (a torsion wire) is suspended in the cup. The cup oscillates through an arc of 4°45′ in either direction, each rotation

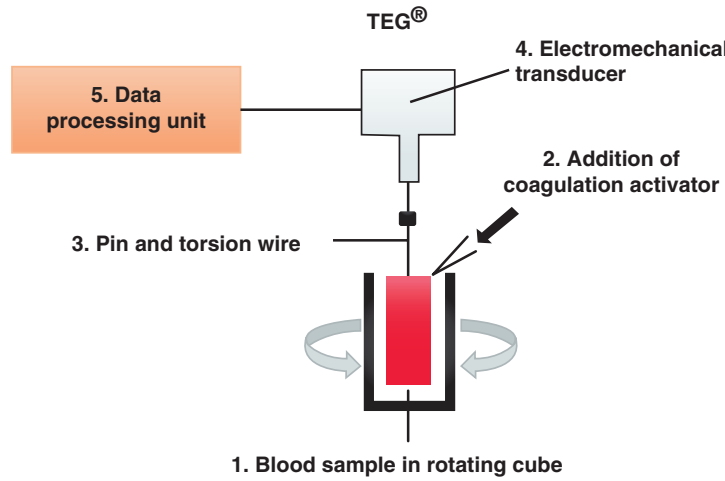


Fig. 18.2 Components of thromboelastography (TEG) instrument

lasting 10 s, aiming to reproduce sluggish venous flow. These mimic low shear conditions similar to those present in the vena cava and well below those seen in venules, small veins and arterial system [19]. Initially the pin remains stationary generating a straight line on the tracing. As the clot begins to form, the pin gets embroiled within the clot and the torque of the cup is transmitted across the pin and the torsion wire to a mechano-electrical transducer [13]. The electric signal thus generated gets converted into a graphic display demonstrating the shear-elastic characteristic of clot (*Y* axis) against time (*X* axis).

The shape provides a rapid assessment of different coagulation states (hypo, normal, hyper) and also provides information regarding specific abnormalities in clot formation and fibrinolysis. A strong clot causes the pin to move directly in phase with the cup creating a broad TEG, whereas a weak clot stretches and delays the arc movement of the pin creating a narrow TEG. As the clot retracts or lyses, the bonds between the cup and pin are broken and the motion is again diminished and eventually stops, depicted by diminishing amplitude followed by a straight line [24].

Various variants of the TEG assay are available to give assessment of tissue factor, effect of heparin, assessment of function fibrinogen as well as platelet functioning (Table 18.2) (Box 18.3).

Table 18.2 Variants of the TEG assay [19, 24]

Kaolin	Contact activation. The standard test is performed with kaolin activator and gives an assessment of overall coagulation
Rapid TEG	Tissue factor and contact activation. Roughly analogous to ACT
HTEG	Kaolin plus Heparinase is used to specifically detect presence of heparin as the enzyme Heparinase will inactivate heparin
Functional fibrinogen	Contains TF (tissue factor) and abciximab that blocks platelet contribution to clot formation and therefore assesses fibrinogen contribution to clot strength
Platelet mapping	TEG platelet mapping assay measures platelet inhibition in comparison with the patient's baseline profile [18]

Box 18.3 Platelet Mapping: Adenosine Diphosphate (ADP) and Arachidonic acid (AA) are used to monitor antiplatelet therapy [18, 24]

A baseline kaolin-activated TEG is done to measure the thrombin-induced clot strength ($MA_{thrombin}$).

After this, a heparinized blood sample to which Reptilase and Factor XIIIa are added to inhibit all effects of thrombin, thus generating a cross-linked fibrin clot demonstrating clot strength coming from fibrin (MA_{fibrin}).

The third and fourth cup require heparinized sample with Reptilase and factor XIIIa (to block thrombin) and activate platelet at the ADP-activated receptor (that thienopyridines or GPIIb/IIIa drugs inhibit) or thromboxane A2 receptor (that aspirin affects) and therefore demonstrate the clot strength which platelets are activated though those specific receptors (MA_{AA} or MA_{ADP}).

Percentage platelet aggregation is calculated by the formula

$$\left[\left(MA_{AA} - MA_{fibrin}\right) / \left(MA_{thrombin} - MA_{fibrin}\right)\right] \times 100.$$

Platelet mapping assay measures clot strength at maximum amplitude and therefore quantifies platelet function. It also measures contribution of ADP and thromboxane A2 receptors to clot formation [16].

Nomenclature of measured values [10, 19].

Quantitative analysis of the TEG is performed by assessment of five main parameters; four related to clot formation and one to clot lysis (Figs. 18.3 and 18.4, Table 18.3).

Reaction (*R*) time—time in minutes taken to reach an amplitude of 2 mm. This corresponds to initial fibrin formation and is related to plasma clotting and inhibitor factor activity.

- Normal range: whole blood: 4–8 min, Kaolin: 3–8 min

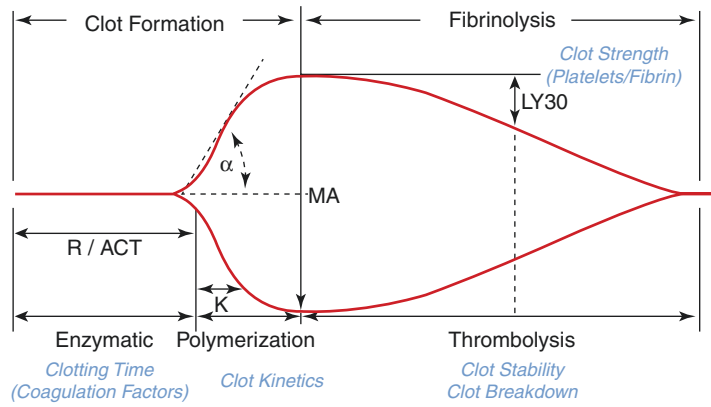


Fig. 18.3 TEG. *R*—reaction time, *K*—amplitude progression from 2 to 20 mm, α—rate of clot formation, MA—maximum amplitude, LY30—clot lysis at 30 min after achieving maximum amplitude

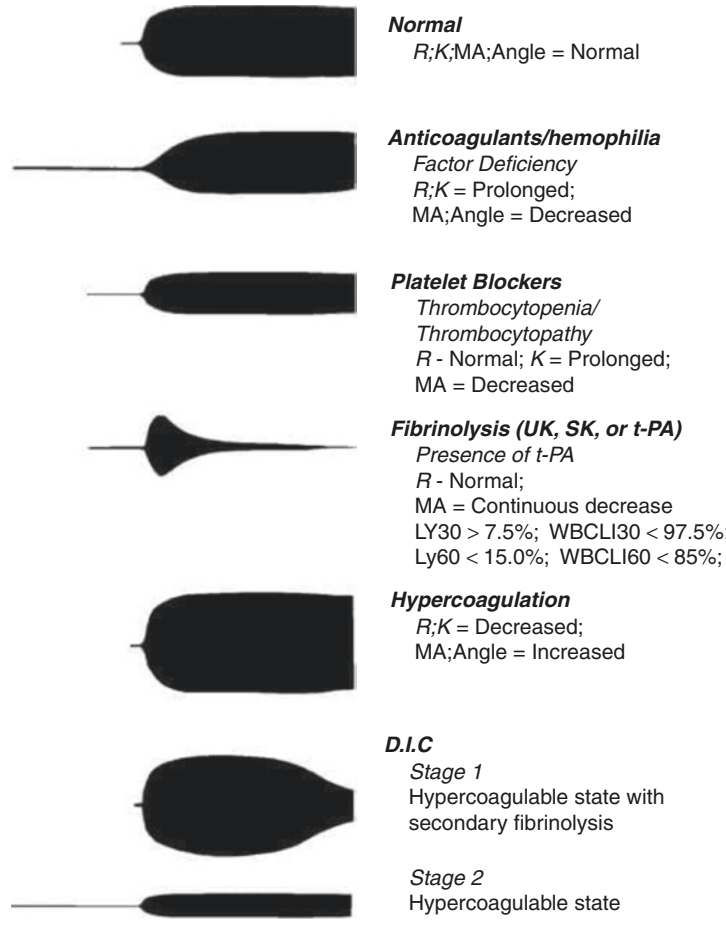


Fig. 18.4 TEG graphs in common conditions

Table 18.3 Derived parameters [19]

CI—clotting index	Global estimation of clot formation using a combination of variables *R*, *K*, MA and *α* angle, calculated continuously
G (shear modulus strength)	Clot strength in TEG represented by computer generated *G* value. $G = (5000 \times \text{amplitude})/(100 - \text{amplitude})$, normal 5.3–12.4 dynes/cm^2 (TEG 11)
E	Elasticity constant—normalized value of *G*
TPI	Thrombodynamic potential index-*E* obtained at maximum amplitude divided by *K* EMA/*K*
CL_{30}, CL_{60}—clot lysis index 30, 60	Measure of lysis calculated as the relationship of amplitudes at 30 and 60 to maximum amplitude
EPL—estimated percent lysis	It is the degree of lysis 30 min after MA is reached, computed 30 s after MA is reached and continuously updated till 30 min after MA is reached [22]

- Prolonged by anticoagulants, factor deficiencies and severe hypofibrinogenaemia
- Reduced by hypercoagulable conditions

Kinetics (*K*) time—time necessary for the clot to reach an amplitude of 20 mm from 2 mm. The *K*-time is a measure of clot formation kinetics.

- Normal range: whole blood: 1–4 min, Kaolin: 1–3 min
- Prolonged by anticoagulants, hypofibrinogenaemia, thrombocytopenia
- Shortened by increased fibrinogen level, increased platelet function

***α* angle**—determined by creating a tangent line from the point of clot initiation (*R*) to the slope of the developing curve. It represents the speed at which solid clot forms and reflects the fibrinogen activity [25].

- Normal range: whole blood: 47–74°, Kaolin: 55–78°
- Increased by increased fibrinogen level, increased platelet function
- Decreased by anticoagulants, hypofibrinogenaemia, thrombocytopenia

MA (maximum amplitude)—is the peak amplitude of the clot. This is the maximum width, in millimetres, reached on the trace and is representative of the maximum strength of the haemostatic plug. It is directly related to the quality of fibrin and platelet interaction. MA is significantly altered by changes in platelet number or function.

- Normal range: whole blood: 50–73 mm, Kaolin: 51–69 mm
- Increased by hypercoagulable states, thrombocytosis
- Decreased by thrombocytopenia, platelet blockers, fibrinolysis, factor deficiencies (lesser extent)

18.4.4.3 Decrease in Amplitude Measurement A30 and A60 [22]

A30—amplitude of the trace 30 min after MA is reached.

A60—amplitude of the trace 60 min after MA is reached.

LY30 and LY 60—percentage reduction in area under TEG curve at 30 and 60 min. LY30 reflects fibrinolysis and measures percent lysis 30 min after MA is reached.

Normal range: 7.5%.

There is another variant of thromboelastography (TEG) available in the name of BIOTEM (Fig. 18.5).

18.4.4.4 Clot Pro

Another viscoelastic analyser is now available in Europe with few modifications to the currently

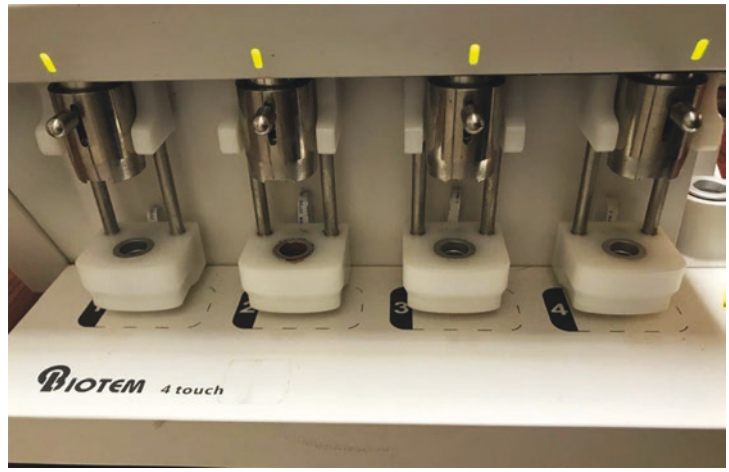


Fig. 18.5 BIOTEM—4 chambers instrument

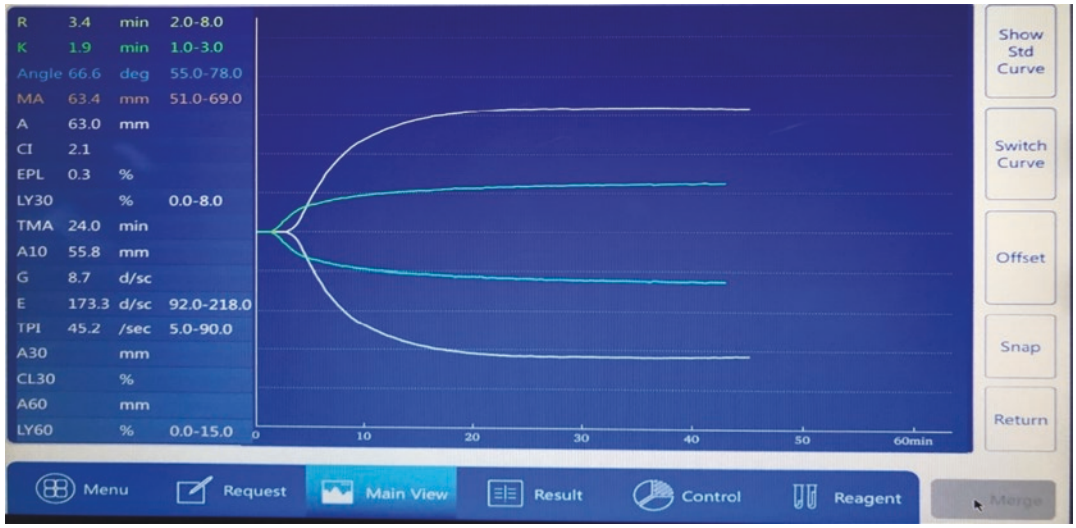


Fig. 18.6 Clot Pro Graph

available analysers. In this analyser they have removed the need to pipette liquid reagents, and these reagents are present in dried form in the pipette itself. When the blood is drawn in through the pipette, the dried reagent present in the sponge of the pipette activates the blood sample (Figs. 18.6 and 18.7). The basic principle of the CLOTPRO is similar to Thromboelastography (TEG), wherein the cup rotates and the pin is static. This design significantly mitigates the potential for error and eliminates reagent handling, which, combined with its ease of use, provides more flexibility and increased throughput in lab-based and clinical settings. ClotPro enables the detection and assessment of factor deficiencies, low fibrinogen, platelet contribution (to whole blood coagulation), heparin and DOAC effects, fibrinolysis and antifibrinolytic drugs [26].

18.4.5 Rotational Thromboelastometry (ROTEM)

Similar to thromboelastography, rotational thromboelastometry (ROTEM) is a viscoelastic whole blood test which analyses the clotting process under low shear conditions and reflects the kinetics of all stages in thrombus formation, clot stability and strength as well as fibrinolysis [16].

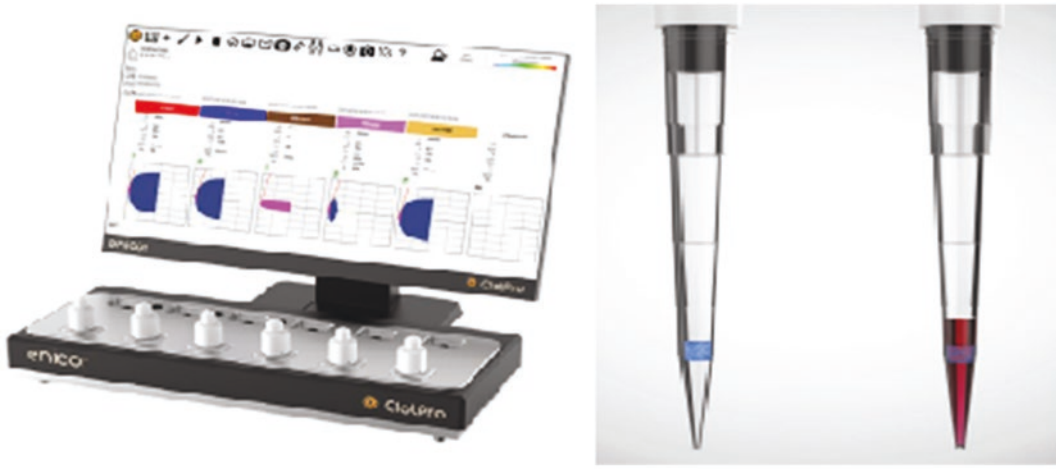


Fig. 18.7 Clot Pro

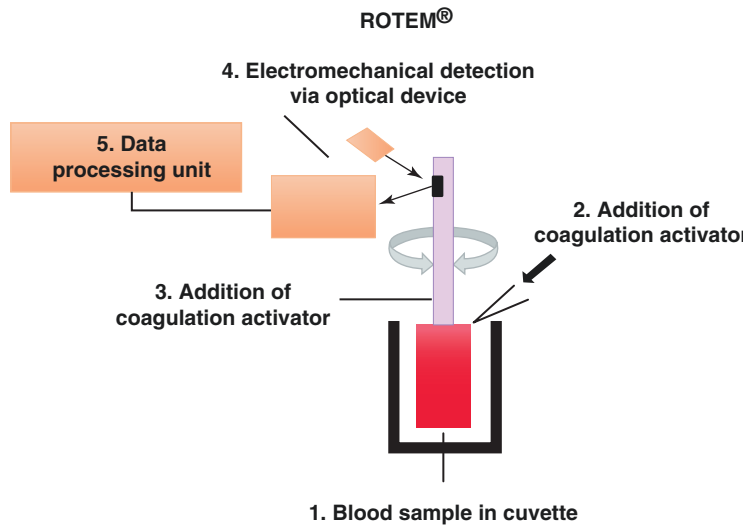


Fig. 18.8 Components of ROTEM instrument

ROTEM is considered to be an improvement of the TEG as there is less vibrational interference. Also, it permits differential diagnosis of underlying patho-mechanism by implementing test modifications. Transfusion requirements after implementation of ROTEM were statistically significantly lower than without, making it a valuable guide in management algorithms (Fig. 18.8).

The ROTEM device uses 300 μL of whole blood with activators incubated at 37° in a heated holder which remains fixed. Activators used are tissue factor in the EXTEM cuvette and contact activator in INTEM cuvette [13, 18, 19]. Care should be taken not to underfill the tubes which may contribute to erroneous values [9, 18]. The difference in the working principle is that the cup is immobile and rotational movement arises from the pin suspended on a ball-bearing mechanism oscillating at 4°75′ every 6 s with a constant force. An optical sensor is attached to the pin (as compared to the torsion wire in the TEG). As fibrin begins to form and the viscoelastic strength of the clot increases, the movement of the pin is impeded, which is detected by an optical system consisting of a light-emitting diode, a mirror on the steel axis and an electronic camera. This is translated into a characteristic trace from which the parameters are assessed.

Nomenclature used in ROTEM [8, 11, 19].

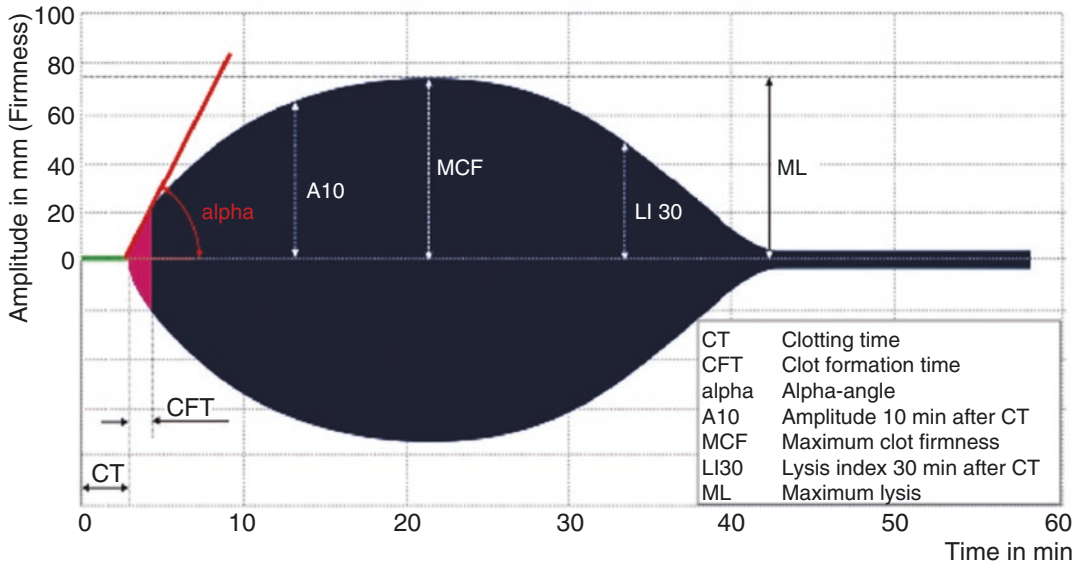


Fig. 18.9 ROTEM graph

Clotting time (CT)—time in minutes taken to reach an amplitude of 2 mm. It is the time to initial fibrin formation and signifies soluble clotting factors in plasma (Fig. 18.9).

- Normal—INTEM: 130–246 s, EXTEM: 42–74 s
- Prolonged by anticoagulants, factor deficiencies and severe hypofibrinogenaemia
- Reduced by hypercoagulable conditions

Clot formation time (CFT)—time necessary for the clot to reach an amplitude of 20 mm from 2 mm. It measures the kinetics of clot formation.

- Normal—INTEM: 40–100 s, EXTEM: 46–148 s
- Prolonged by anticoagulants, hypofibrinogenaemia, thrombocytopenia
- Shortened by increased fibrinogen level, increased platelet function

***α* angle**—angle between tangent to a tracing at 2 mm amplitude and horizontal line. Relates to rapidity of fibrin cross-polymerization

- Normal—INTEM: 71–82°, EXTEM: 63–83°
- Increased by increased fibrinogen level, increased platelet function
- Decreased by anticoagulants, hypofibrinogenaemia, thrombocytopenia

Maximum clot firmness (MCF)—Greatest vertical height of tracing or the peak amplitude. Depicts stability and strength of the clot and platelet number and function.

EXTEM is a baseline test which supports rapid generation of a clot. The MCF_{extem} gives information on clot strength and stability which depends on platelet and fibrinogen level. The FIBTEM test used a platelet inhibitor and therefore MCF_{fibtem} gives an insight to the fibrinogen contribution to the clot. Therefore, comparing these two values can help differentiate platelet-related issues from hypofibrinogenaemia. A low MCF_{fibtem} is indicative of fibrinogen transfusion and a normal MCF_{fibtem} in presence of a low MCF_{extem} would be indicative of need of platelets.

- Normal—INTEM: 52–72 mm, EXTEM: 49–71 mm
- Increased by hypercoagulable states, thrombocytosis
- Decreased by thrombocytopenia, platelet blockers, fibrinolysis, factor deficiencies (lesser extent)

Lysis Index 30 (LI30) is the percent reduction in MCF that exists whose amplitude is measured

30 min after CT is detected. Depicts clot stability and fibrinolysis (Box 18.4).

Box 18.4 ROTEM ASSAYS [19, 24]

INTEM—Contact activation. Reagent containing phospholipid and ellagic acid as activators. This provides information similar to the aPTT (intrinsic pathway).

Assessment of clot formation and fibrin polymerization

EXTEM—Tissue factor activation. Reagent contains tissue factor and provides information similar to PT (extrinsic pathway).

Fast assessment of clot formation and fibrinolysis

HEPTEM—Contains lyophilized heparinase for neutralizing unfractionated heparin, basically a modified INTEM by adding heparinase to inactivate present heparin.

To analyse heparin effect

APTEM—Contains aprotinin in addition to tissue factor. Used together with EXTEM.

Fast detection of fibrinolysis

FIBTEM—Uses cytochalasin D which blocks platelet contribution to the clot formation. When compared to the EXTEM analysis, it allows qualitative assay of fibrinogen contribution to clot strength.

Measure of functional fibrinogen levels

NATEM—Native whole blood sample—impractical and not used due to long CFT time.

The TEG is capable of analysing two samples at a time whereas ROTEM can analyse four samples simultaneously.

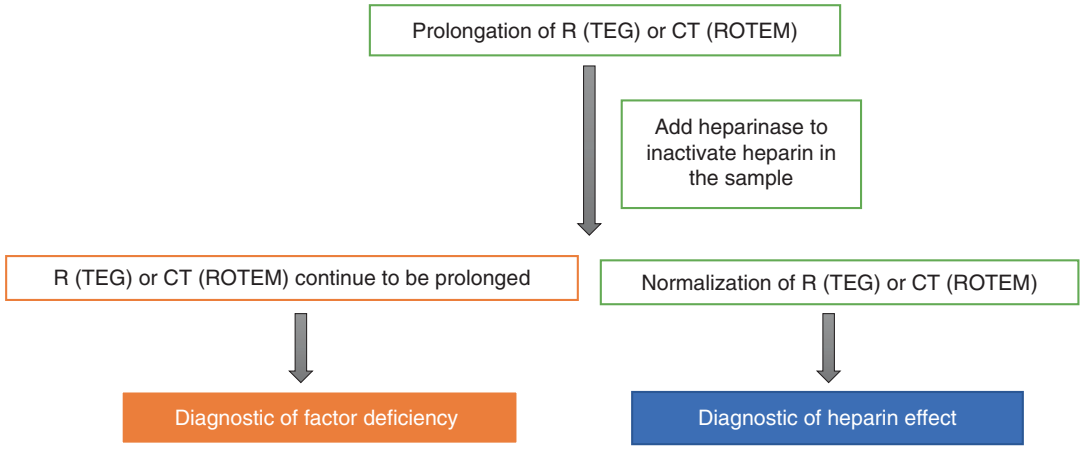
The traces of TEG and ROTEM appear similar; however, it is important to remember that terminologies and reference ranges are unique to each device and not interchangeable (Table 18.4). The differences may be explained due to different cups and pins used in both systems—ROTEM cups are composed of plastic with greater surface charge which may result in greater contact activation. There is also a variability in the activators and reagents used contributing to the significant difference in their results.

Table 18.4 Operating characteristics of TEG and ROTEM [19]

Characteristics	TEG	ROTEM
Pipetting	Manual	Automated
Cup motion	Moving	Fixed
Pin motion	Fixed	Moving
Angle of rotation	4°45′/5 s	4°75′/6 s
Detection	Pin transduction	Impedance of rotation
Temperature control	24–40	30–40
Cup interior	Smooth	Ridged (thickness 0.6–0.9 mm)
Cup material	Cryolite (acrylic polymer)	Polymethylmethacrylate

18.4.5.1 Diagnostic Power of TEG/ ROTEM [11]

1. *Heparin effect/factor deficiency*



2. *Clot firmness*

Strength of clot is determined by

(a) Fibrinogen
(b) Platelets
(c) Factor XIII (by assay)

ROTEM can be efficiently used to differentiate the cause of bleeding.

FIBTEM and EXTEM are performed simultaneously [11, 27] (Fig. 18.10).

The MCFextem gives information on clot strength and stability which depend on platelet and fibrinogen level.

MCFfibtem gives an insight to the fibrinogen contribution to the clot.

Therefore, comparing these two values can help differentiate platelet-related issues from hypofibrinogenaemia. A low MCFfibtem is indicative of fibrinogen transfusion and a normal MCFfibtem in presence of a low MCFextem would be indicative of need of platelets.

In TEG

Decreased α and prolonged K will signify fibrinogen deficiency and decreased MA will signify platelet deficiency.

3. *Hyperfibrinolysis*

TEG and ROTEM are considered the gold standard for diagnosis of hyperfibrinolysis by measuring lysis.

Example: in a case of severe hyperfibrinolysis, there may be no clot formation with the EXTEM. Addition of aprotinin and performing APTEM will trigger clotting by inhibiting the fibrinolytic component, thus demonstrating the presence of fibrinolysis. If the MCF of APTEM is reduced, thrombocytopenia may also coexist with hyperfibrinolysis.

18.4.6 The Sonoclot

The sonoclot analyser was introduced by von Kaulla et al. in 1975 as a modality of measuring viscoelastic changes in whole blood [28, 29]. The entire haemostatic process is measured and depicted in the form of a graph known as Sonoclot signature (Fig. 18.11a, b).

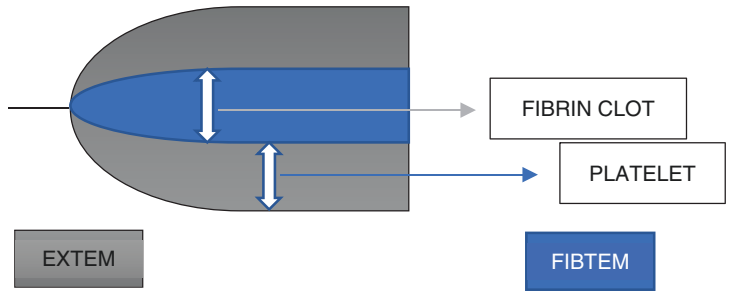


Fig. 18.10 ROTEM in use—FIBTEM

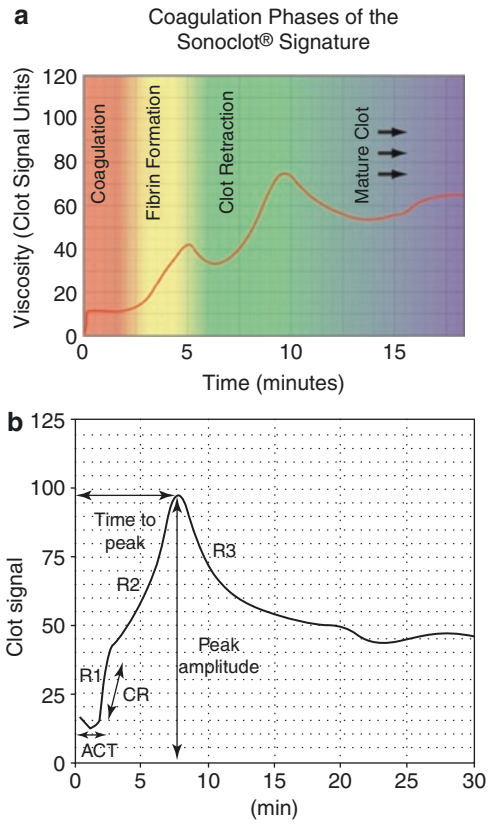


Fig. 18.11 (**a**) Sonoclot. (**b**) Sonoclot showing different components—ACT, R1, R2, R3 and Peak amplitude

18.4.6.1 Principle

The analyser consists of a hollow open-ended disposable probe, vibrating vertically at a distance of 1 µm at a frequency of 200 Hz, mounted on an ultrasonic transducer. This is immersed to a depth in a cuvette containing 0.4 mL of whole blood which exerts a viscous drag on probe, impeding its free vibration. As fibrin strands begin to form and the sample begins to clot, the drag on the probe increases further, effectively increasing the mass of the probe. This increase in impedance is sensed by the electronic circuit and converted to an output signal on a paper in the form of a curve describing the whole process from the start of fibrin formation, through polymerization of the fibrin monomer, platelet interaction and eventually clot and lysis. Usually a plain cuvette is used, without an activator, to derive sonoclot signature [13]. However, two other types of cuvettes, both containing celite activator, are better suited for intraoperative monitoring (the red cap tube contains low concentration and white cap tube contains high concentration of the activator).

The graph is plotted on a 100 mm wide recorder chart with *X* axis in minutes and *Y* axis as clot signal.

Measurements obtained [28]:

Sonoclot activated clotting time (SONACT)—time taken for upward deflection of 1 mm. It represents time (in seconds) for fibrin formation. It corresponds to ACT. Range 85–145 s without heparin.

Clot rate (CR)—rate (units/minute) of fibrin formation (from fibrinogen) depicted by the gradient of primary slope R1. The rate can also be expressed as a percentage of the peak amplitude per unit time—15–45% being normal.

An inflection point can be seen between R1 and R2 representing the start of contraction of fibrin strands by the action of platelets.

Secondary slope R2—represents further fibrinogenesis, fibrin polymerization and platelet-fibrin interaction.

R2 peak (PEAK)—indicates completion of fibrin formation. It has two variables:

- Time to peak (in minutes)—index rate of conversion of fibrinogen to fibrin (<30 min)
- Peak amplitude (in units)—index of fibrinogen concentration

Downward slope R3—represents platelets induced contraction of completed clot after which the clot mass decreases as the serum is squeezed out of clot matrix. Low platelets and/or poor function produce a shallow R3. Decreased signal of R3 will represent fibrinolysis.

Platelet function (PF)—the slope gradient of R3 represents the number of platelets and level of platelet function and is recorded as PF by the analyser.

The signal decreases further as fibrinolysis takes place and eventually returns to pre-immersion values which is seen only in patients with accelerated fibrinolysis. Therefore, the decrease in signal after R3 slope is the measure of fibrinolysis (Box 18.5).

Box 18.5 Variations of Sonoclot [8]

SonACT with celite activator for rapid assessment

k-ACT with kaolin activator for heparin management

gb-ACT + glass beads—overall coagulation and platelet function assessment

gb-ACT + glass beads + heparinase—assessment in presence of heparin

The results are influenced by age, sex and platelet count and have shown poor reproducibility. However, some studies have demonstrated the sonoclot analyser's precision to be quite comparable to that of thromboelastography [16].

18.4.7 Use of Standard/Conventional Tests in Liver Transplant

Routine coagulation tests have not been found to be accurate to predict bleeding events in patients with cirrhosis. PT/INR and aPTT are sensitive to procoagulant factors and do not account for anticoagulant factors. Moreover, they are performed in plasma and do not reflect the interaction of cellular components, vascular endothelium and fibrinolytic systems [8].

The standard laboratory tests have a long turnaround time which may not be appropriate for timely intervention often warranted during liver transplant surgery. They do not offer a differential diagnosis of impaired haemostasis and therefore may be inadequate to specify which component therapy is indicated.

Due to these shortcomings, standard laboratory tests have made way for the use of point-of-care viscoelastic coagulation monitoring devices during liver transplant.

18.4.8 Use of Point-of-Care (POC) Devices in Liver Transplant

Intraoperative red cell transfusion (>10 units) was found to be an independent risk factor for in-hospital mortality after liver transplant in a multivariate analysis by Li et al. [8]. Transfusion of ≥3 units PRBC (packet red blood cell) and ≥3 units FFP (fresh frozen plasma) was independently associated with poor graft survival at 1 and 5 years [30]. Platelet transfusion causing acute lung injury which ultimately contributes to mortality has also been mentioned in the literature.

There is evidence that point-of-care guided factor replacement aids in reducing red cell as well as volume of plasma transfusion during liver transplantation [2]. In fact, the reduction of FFP has been found to be >90% and there have been reports of significant reduction in incidence of massive transfusion. This surely translates into benefit with respect to both risk-benefit ratio and cost-effectiveness [8].

Data also suggests that these devices are reflective of the rebalanced haemostasis which has been described in cirrhotic patients and evidence, albeit limited, suggests that patients with compensated cirrhosis often maintain normal global haemostasis. There are no prospective studies validating the accuracy of TEG or

ROTEM for predicting procedural bleeding in cirrhotic patients.

Transfusion of blood during liver transplant has been thought to be inevitable. TEG-guided component therapy was described in 1985 for the first time and has been a topic of interest thereafter given the fact that minimizing transfusion will always have beneficial effect on outcome. Using parameters such as an increased *R*-time which reflects time to fibrin formation, as an indicator for fresh frozen plasma transfusion, decreased angle denotes a requirement of cryoprecipitate as it indicates speed of clot formation, decreased MA which denotes the clot strength is indicative of platelet transfusion—a reduction of transfusion was demonstrated [9].

18.4.8.1 Pre-transplant Liver Failure Patients

TEG values and standard laboratory tests in the preoperative period do not corelate on a consistent basis. These patients had deranged PT, INR and aPTT which was not consistent with the finding on TEG which corelated with the clinical picture [31]. Studies found that TEG-based algorithms are superior to conventional lab tests such as INR, fibrinogen and platelet count to guide transfusion [23]. There have been descriptions of patients with high INRs and MELD score with haemostatic profile ranging from normal to hypercoagulable [32]. MA of less than 47 mm was found to have 90% sensitivity and 72% specificity to predict the need for massive transfusion [3, 33].

18.4.8.2 Intraoperative Use of TEG During Liver Transplant

Studies have demonstrated a significant reduction in transfusion volume compared to a cohort of patients transplanted prior to development of the protocol. Kang and many authors have demonstrated that viscoelastic testing can offer valuable insight and potentially guide transfusions [34]. Patients who underwent liver transplant with a stringent transfusion protocol received fewer plasma transfusions than patients who underwent transfusion based on less extreme TEG values [35]. Patients who underwent POC testing and were managed by algorithms based on these received significantly lower platelet concentrate transfusion rate as well as less packed red cell transfusions [20, 36] (Table 18.5). POC group had fewer thrombotic complications. There was no significant difference in perioperative mortality and no beneficial effect on mortality could be demonstrated either [17].

TEG has also been useful in detecting hyperfibrinolysis and therefore guiding antifibrinolytic therapy during liver transplant thus limiting empirical use of these drugs and thereby reducing incidence of thrombotic episodes.

Another study comparing ROTEM-based protocols demonstrated that there were reduced red blood cell transfusion and decreased complication rates with these patients. ROTEM was also efficient in picking up hyperfibrinolysis during reperfusion phase. While TEG and sonoclot provide a global picture of haemostasis, ROTEM offers a number of test variants which facilitate differential diagnosis.

Use of a TEG-based transfusion algorithm intraoperatively during liver transplant had no adverse effect on survival at 30 days and 6 months after liver transplant [37] (Fig. 18.12). Perioperative TEG values also have potential value at predicting outcomes from liver transplants. TEG values obtained preoperatively could be valuable in predicting early hepatic artery thrombosis following liver transplant [38].

An example of how POC viscoelastic tests can be used to manage transfusion.

Table 18.5 Transfusion triggers generally used in liver transplant [8]

	Trigger for FFP	Trigger for platelet	Trigger for fibrinogen
TEG	$R > 14$ min	MA < 45 mm	
ROTEM	$CT_{intem} > 4$ min	$MCF_{intem} < 45$ mm	$MCF_{fibtem} < 8$ mm
		With $MCF_{fibtem} > 8$ mm	
		Or $MCF_{intem} < 25$ mm	
Conventional tests	INR > 1.5	Platelet $<50 \times 10^9$/dL	Fibrinogen <1 g/dL

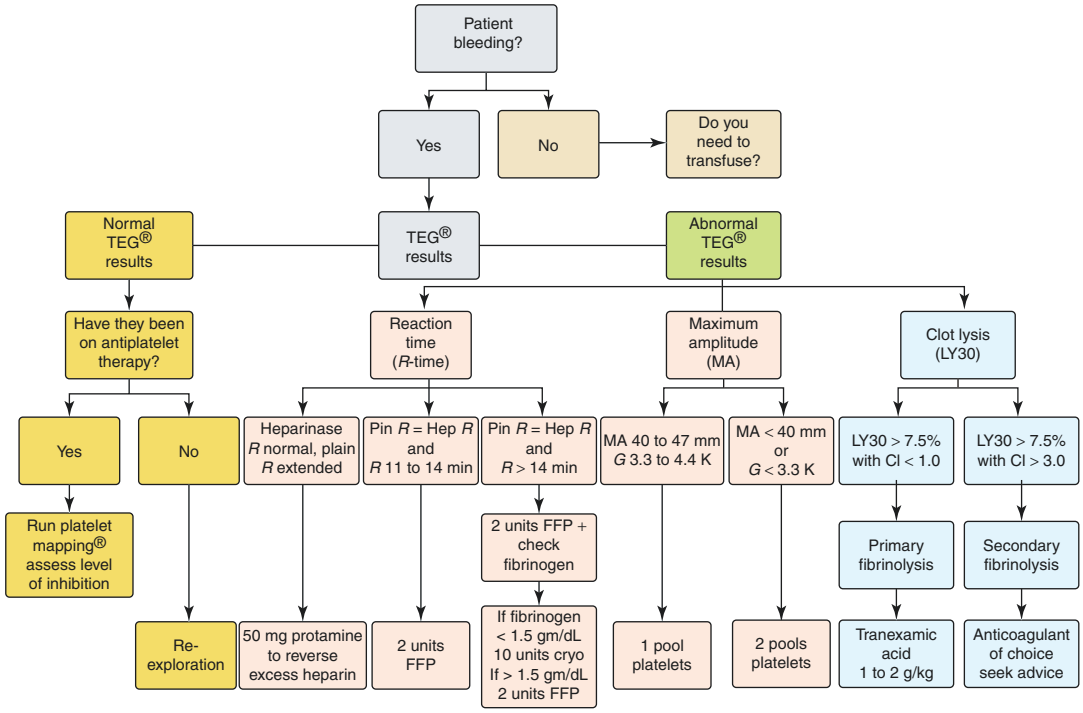


Fig. 18.12 Algorithm using viscoelastic test for transfusion management

18.4.8.3 Sonoclot in Liver Transplant

Though the literation is not extensive, Sonoclot has been used in liver transplant surgery and diagnosis of platelet dysfunction or clotting factor deficiency correlated well with clinical scenario. It has been shown to be sensitive compared to laboratory tests in detecting platelet dysfunction and fibrinolysis as well [16, 29].

18.4.8.4 Application of Platelet Function Testing in Liver Transplant [8]

In patients with hypercoagulable states (such as Budd-Chiari syndrome) coming for transplant, prevention of postoperative thrombotic events is crucial for which antiplatelet therapy has to be instituted at the earliest. Thromboelastography has been reported to be less accurate in detecting hypercoagulable states as compared to hypocoagulable states. Therefore, platelet mapping may be synergistic in managing perioperative coagulopathy in hypercoagulable cirrhosis patients during liver transplant.

18.4.9 Limitations [23]

TEG requires daily calibration (two or three times a day calibration of the machine is recommended).

Point-of-care machines do not undergo same quality testing and evaluation processes like those of conventional tests.

It is imperative that some kind of training be given for anyone performing the test. Standard technique with adherence to time guidelines must be complied with.

Though meaningful information can be obtained in 10 min of initiating the test, the whole test takes 30–60 min to complete.

Reagent sensitivity may differ between manufacturers.

Equipment, activators and other test modifications alter the specificity of the test and make inter-laboratory standardization a distant possibility, therefore limiting comparison of results [16].

Another limitation of TEG was inability to detect platelet impairment due to antiplatelet

drugs which was later overcome by platelet mapping.

Bacterial infections in cirrhotics may trigger release of heparin-like substances which may be demonstrated as a prolonged R-time in the TEG. This would require antibiotic therapy rather than product administration [2].

The coagulation profile in cirrhotic patients is a dynamic process rather than a static one; therefore, TEG/ROTEM done at the baseline may not reflect and predict the risk of bleeding or thrombosis over a longer period of time [17]. Having said that, it would not be reasonable to perform repeated assessments during the entire hospitalization as the cost associated with this may not be justified.

There is a plethora of literature indicating the lack of utility of traditional laboratory tests; however, studies and evidence available to ascertain utility and efficiency of point-of-care monitoring are still not substantial. Prospective, randomized studies are required to strengthen the evidence of its use [17].

Viscoelastic tests do not detect the effects of hypothermia as the sample is measured at 37°. Neither do they test the effect of hypocalcaemia on clot strength and platelet function [30].

Nuances of the tests, such as use of reagents and stimulators and analysis of the traces obtained, are still not well-defined and standardized and have subjective variability [4].

No beneficial effect of POC-based coagulation has been demonstrated on postoperative mortality [16].

Results of the sonoclot are influenced by factors such as age, sex and platelet count, and it has been criticized for the same. The sonoclot analyser's role may be limited in acutely bleeding patients, and its application may be limited to goal-directed management algorithms [16] (Box 18.6).

Box 18.6 Summary

Pathophysiologically speaking, coagulation can be broken down into [20]:

- Primary hemostasis
- Thrombin generation
- Clot formation/stabilization
- Fibrinolysis

Most standard laboratory tests reflect only time to fibrin formation while others are only quantitative and therefore do not reflect the entire clotting process [39].

Viscoelastic tests are useful in measuring time until clot formation, dynamics of clot formation and stability and integrity of the clot over time.

These tests have been used in liver transplantations and there is evidence to show that transfusion protocols based on point-of-care tests have reduced red cell and plasma transfusion and therefore contributed to reduction in complications due to transfusion.

There is evidence that point-of-care monitoring also reduces the incidence of postoperative thrombotic complications, and this is especially of importance in cirrhotic patients undergoing transplant.

Literature does not indicate effect of POC testing on perioperative mortality [16].

While TEG and sonoclot describe the global picture of hemostasis, ROTEM has a repertoire of test variations which enable a differential diagnosis [16].

Some studies correlating POC devices with standard laboratory tests found that MA correlates with both platelet count and fibrinogen concentration in hypercoagula-

ble patients, a significant correlation between PTT and R-time and euglobulin clot lysis time and lysis time, while other studies demonstrated poor correlation between these [9, 23].

More evidence, in the form of randomized trials, regarding key issues such as standardization, algorithms, outcomes and economic viability, is required.

The motto of management of coagulation in a bleeding patient is to replace what is missing in a timely efficient manner and in transplant recipients; this is best achieved by using point-of-care monitoring devices.

18.5 Conclusion

Bleeding in liver failure patients is a unique and multifactorial phenomenon, and it is important to understand the rebalanced haemostasis occurring in these patients. Conventional testing may be inappropriate in these patients and the use of point-of-care coagulation testing has emerged as a valuable adjunct in establishing goal-directed transfusion of blood products. Transfusion of blood and blood products has been significantly reduced, and this has a major impact on postoperative complications and morbidity following liver transplant. These techniques should be advocated more routinely as there is evidence to suggest that there is a scope for increasing their implementation.

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