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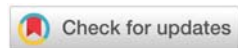
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Review Article

New methods for bleeding monitoring

Abstract

Bleeding is a potentially preventable reason of the death among patients during major surgery. Appropriate monitorization is necessary to perform optimum resuscitation. However, conventional coagulation tests have some limitations. In recent years, point of care (POC) tests has been developed to improve patient safety in the presence of clinical bleeding POC tests measure viscoelastic properties of full-thickness clot formation in the beginning of bleeding. In this review, both of advantage and disadvantage of monitorization tests during bleeding management is explained.

Introduction

Bleeding is one of the feared complication especially in patients undergoing consecutive anesthesia and invasive surgical procedures [1,2]. Routine laboratory coagulation tests and measurement of platelet count are the most commonly used methods to define coagulation status of the patient. However, there are some limitations with conventional tests, point of care (POC) tests developed to overcome with these limitations [2].

The main goal of anesthesiologist is to prevent deterioration of hemostasis due to bleeding and bleeding complications and reduce the rate of morbidity and mortality [3,4]. The causes of perioperative bleeding may include platelet dysfunction, excessive fibrinolysis, hypothermia, preoperative anemia, lack of coagulation factors, or dilution. Among those, hyperfibrinolysis is also most important factor in the development of post-traumatic coagulopathy [3]. Bleeding monitorization is required to patient-specific transfusion planning and to avoid undesirable effects of excessive volume, otherwise increase the perioperative complications and risks due to unnecessary allogeneic blood transfusions [5]. Although there is no internationally accepted management protocol in bleeding patients, algorithm-based transfusion protocols depend on POC tests produce better results than individual decisions [6].

Bleeding monitoring should consist of the patient's history of bleeding and laboratory tests to reveal increased bleeding risk but cannot exclude exogenous factors [7]. Guidelines for management of bleeding monitorization suggest that the amount of platelet, activated partial thromboplastin time (a PTT), prothrombin time (PT), and fibrinogen levels should be measured [3].

History of coagulation tests

Prothrombin time was developed by Armand Quick in 1935 to evaluate liver disease, which shows the extrinsic pathway in the recalcified, citrated blood sample with the addition of tissue thromboplastin and the first formation of the clot form [8,9].

Activated partial thromboplastin (a PTT) time was first developed in 1953 and modified in 1961. A PTT reflects the time required for clot formation in seconds, when the plasma is mixed with negatively charged phospholipids and particulate or soluble activators of contact coagulation factors.

The history of the viscoelastic tests coincides with the beginning of the 20th century and the first prototype was thromboelastographic, introduced by Hastert in 1948 and developed by Haemonetics [10-12]. It evaluate initially coagulation factor deficiencies detection, later anticoagulant effect, thrombocytopenia, and fibrinolysis and we could have information about the formation of the clot, the kinetics, the stability of the clot [13,14]. More information on the quality of coagulation than quantitative (numerical) values is available [11].

Rotational thromboelastometry (ROTEM) is a compact, portable point-of-care instrument introduced in 1995 [15]. The working principle is like thromboelastography and there are slight differences between them [16].

The Sonoclot analyzer was used in 1975 by Kaulla et al. It also detect viscoelastic changes in either the whole blood or in the plasma [2].

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Coagulation cascade

The cell-based coagulation cascade model consists of a series of complex cellular and biochemical reactions. However routine plasma-based coagulation tests ignore cellular component of coagulation, so they are inadequate to solve bleeding problems [4].

The extrinsic pathway begins with the release of the tissue factor and allows the Factor (F)X to become active by activating the FVII. Whereas the extrinsic pathway is activated after the tissue damage, the intrinsic pathway begins as a result of damage to the blood vessels. The intrinsic pathway activates factor XII, which released after contact to the damaged vessel surface with blood, and eventually activates the FX, resulting in the activation of FXI and FIX.

Activation of FX allows the common pathway to be reached. In this way, thrombin enters the circuit. Activation of FX causes prothrombin to form into thrombin and on this acts on the fibrin. At the same time, thrombin activates FXIII, which leads to the formation of cross-linked fibrin strands.

The formation of fibrin polymers also constitutes the place where standard coagulation tests can not reveal further monitoring. Thromboelastographic has a unique ability to measure the strength of the platelet-fibrin binding and the development of the clot.

Standard-bedside coagulation tests

Standard laboratory tests such as activated partial thromboplastin time and prothrombin time give the results obtained from the patient's plasma and do not account for other items of coagulation such as platelets and fibrin [5]. While tests such as platelet count, platelet aggregation and Clauss fibrinogen measurements, and fibrin degradation products can assess individual items of coagulation, but it does not take account of interactions in blood and contributions of the cellular content [17,18]. Those do not involve multifactorial states such as endothelial effects in clot formation, interactions of platelets with each other, and subsequent thrombin formation, and fibrinolysis. Many laboratories can provide these tests and can be used to predict transfusion and mortality [18].

While the PT measurement shows hereditary or acquired deficiencies of FII, V, VII, X and fibrinogen; aPTT measurement reveals FVIII, FIX and FXI deficiencies and the use of anticoagulants of direct action type [8]. The aPTT measurement shows the intrinsic pathway and common pathway whereas PT measures the extrinsic pathway and common pathway. In patients with ongoing hemorrhage, the PT measurement is superior than a PTT, due to better correlation and the absence of interaction with many situations [19].

Although standard laboratory tests are the most commonly used for bleeding monitorization, the accuracy of bleeding monitorization has not been fully demonstrated [14].

Standard laboratory tests are both time consuming and useless with long time results nearly 45 min, especially in trauma patients, which rapid evaluations are needed in the first hours [19]. Conversely, bedside viscoelastic tests can provide qualitative assessment of patients' coagulation status within 5-10 minutes. Hyperfibrinolysis conditions cannot be measured by standard tests. However hyperfibrinolysis in trauma patients is associated with poor prognosis [3,19]. Conventional tests are insufficient to investigate the acquired deficiencies of pro- and anti-coagulants due to thrombomodulin [1].

Fibrinogen is the first depleted factor in the massive hemorrhagies, which is the basis of effective coagulation. Concentration can be measured indirectly by the Clauss method. Fibrinogen is proportional to the clotting time and is measured using calibration standards.

Standard- bedside tests do not involve hematocrit effect in efficacious plasma volume in measurements.

Point of care tests

Point-of-care tests (sonoclot, thromboelastography [TEG] and rotational thromboelastometry [ROTEM]) can measure the viscoelastic properties of full-thickness clot allowing bedside assessment of the secondary hemostasis of blood clotting (10). Unlike standard tests, full screening can be provided faster with small volume of samples and give the true image of clot formation [17]. They can be used in cardiovascular surgery and liver operations besides trauma patients.

Point-of-care tests, or otherwise bedside tests have been shown to benefit for rapid clinical decision-making and have been developed especially in the last decade [20]. These tests are particularly important because they can be performed close to the patient and provide information about the quality and dynamics of the clot [16]. In contemporary practice, 2 devices are at the forefront. The older version of the TEG instrument (Haemoscope Corporation, Niles, IL, USA) and the new ROTEM (Pentapharm GmbH, Munich, Germany). The most important feature of Viscoelastic Monitoring (VEM) devices is the viscoelastic properties of full-blood clot formation. The firmer the clot is, the higher the force that the device measures against the rotation or vibrating movements VEM devices can also be adapted to body temperature. While TEG shows clot strength, it can help to distinguish between a problem developing in clot formation or a mechanical event [21]. VEM can display not only the fibrin polymers formation time but also the situation after clot formation.

TEG can give qualitative and quantitative measure of the physical properties of the clot [22]. The thromboelastogram device consists essentially of an electromagnetic transducer, a cylindrical cuvette containing blood, and fixed needle segments. Calcium chloride, kaolin and phospholipid are placed in the cuvette together with citrated whole blood so that the fibrin-thrombocyte ligatures are attached to the needle blood sample and the rotation movements in the cuvette are transferred onto the needle. The needle stays suspended in the blood and is converted into electrical signals by means of an electromagnetic transducer as the blood clotting begins. The rate and strength of fibrin-platelet formation affects the magnitude of the needle movement and the signal amplitude. There is little difference between ROTEM and TEG, although it

depends on the same principles and gives the same graphical chart [16]. These differences include optical detection system, immobilization of the cuvette, and oscillation of the needle / wire system.

When ROTEM delta analyzes each parameter on separate channels, the TEG 6 and ROTEM sigma analyzes at the same time. TEG is used coalin, EXTEM is used tissue factor, and INTEM is used contact activator ellagic acid as activator [16].

There are 6 major outcomes. R time, K time, alpha angle, maximum amplitude, G value and lysis rate. Maximum amplitude is the thrombocyte-fibrin clot strength, which is influenced by changes in fibrinogen and platelet count and function. The reaction time (R) indicates the start of the enzymatic clot process and indicates the time interval between the start of the test and the formation of fibrin or clot until 2 mm of the nucleus occurs. G (dyne / cm2) gives platelet brittleness, platelet and enzymatic contribution to clot strength and maximal amplitude can be calculated together. Angle (α) is a reflection of fibrinogen activity so that the rate of formation of fibrin covalent bonds can be examined by the rate of clot formation.

The active coagulation time, R time and kinetic time are correlated with PT, INR and aPTT, while alpha angle correlates with platelet count. The prolongation of R shows hemodilution, endogenous heparin release due to tissue brittleness, and lack of coagulation factors. In the case of hypercoagulation, shortening of R time is observed.

Kinetic time (K time, TEG) or coagulation time (ROTEM) indicates the time to form an amplitude of 20 mm and indicates the time taken for the formation of stable fibrin [23]. Fibrinogen delivery is the treatment of an extended period of K time. A short K time indicates rapid formation of clot and indicates rapid consumption of hyper coagulation or coagulation factors.

The decrease in maximum amplitude indicates a decrease or worsening in hyperfibrinogenemia or platelet function. Alfa angle and maximum amplitude correlate with coagulation factor levels, fibrinogen concentration, and platelet count. Thromboelastographic remains at maximum amplitude for a significant period of time, but decreases when the clot lysis begins. The machine itself calculates this and sets a rate.

Coagulation time in TEG and ROTEM is used as triggers for fresh frozen plasma transfusion, although they show a complete correlation with PT and a PTT time [24]. Most importantly, these values can be attributed to reduced levels of fibrinogen, cellular components or patients receiving warfarin therapy, and reduced antithrombin levels due to hemodilution.

Point of care (POC) tests do not compromise precision and sensitivity while achieving fast results. POC tests have significant advantages with ease of use, quick results and benefits in the use of blood and blood products. A graph plotter that occurs over a period of time in both tests provides information about clot tension.

TEG can work in 4 different ways; standard, accelerated version of the standard test (r TEG), heparinase version and platelet mapping method. R TEG is a rapid test that we can

examine intrinsic and extrinsic pathways. Heparinase TEG is effective in the effect of residual heparin in coagulation. The platelet mapping method is used pharmacologically to quantify platelet inhibition.

Thromboelastometry (TEM) is the common name for many methods, each of which uses TEM as suffix. FIBTEM is used to assess the effect of fibrinogen in clot formation, APTEM hyperfibrinolysis, and HEPTEM residual heparin in coagulation, INTEM for the intrinsic pathway, EXTEM extrinsic pathway control and a need for rapid evaluation [25]. Simple hepatic TEG and ROTEM with heparinase addition has been developed to permit monitoring of heparinized patients. With further improvement of in vitro conditions, values such as a PTT (INTEM, kaolin-based TEG), PT (EXTEM, r TEG) and fibrinogen (FIBTEM, functional fibrinogen TEG) can be reached. In previous studies fibrinogen levels <1.5 g.l-1 reached a threshold value of 1.5-2.0 g.l-1 when starting treatment.

FIBTEM and functional fibrinogen TEG can provide a direct measure of the contribution of fibrinogen to clot strength. Despite a normal FIBTEM, low EXTEM suggests a deficiency or dysfunction of the platelets [26]. PT, a PTT, fibrinogen and platelet levels correlate with ROTEM, EXTEM, INTEM and FIBTEM.

In cases of bleeding or thrombosis, difficulty in determining the risk of bleeding or thrombosis due to complex relationships between hemostatic and fibrinolytic proteins, as well as difficulty in directly measuring fibrinolysis [27]. Although both TEG and ROTEM may show systemic fibrinolysis, it is difficult to see this in cardiovascular surgery when ε-aminocaproic acid or tranexamic acid is routinely used. Nevertheless, after major surgeons, hyperfibrinolysis is a parameter that can increase mortality [28]. The most promising development in TEG and ROTEM is the development of early goal-directed therapy by these devices.

Sonoclot (Sienco, Denver, CO, USA) analyzer can also give both quantitative and qualitative information about the entire haemostasis process allowing the evaluation of viscoelastic properties of whole blood with a vertically vibrating probe [2,6]. To initiate a measurement, the hollow, open-ended disposable plastic probe is mounted on the transducer's head. The sample is then supplemented with various coagulation activator / inhibitor-containing cuvettes. After automatic mixing, the probe is immersed in the sample and makes a vertical oscillating motion. Impedance changes during clot formation are measured. Sonoclot signature provides active coagulation time, clotting rate and qualitative assessment of platelet function. It may show better the early phases of fibrin formation when compared to PT and a PTT [17].

The Point of care device CoaguChek (Roche Diagnostics, Mannheim, Germany), used to provide out-of-hospital measurements of patients receiving oral vitamin K antagonists, correlates with PT measurements in standard laboratory [29]. Since the use of these tests does not require a special coagulation laboratory or an experienced laboratory staff, it can also be used in the operating room, intensive care unit and emergency clinic. When surgical procedures are considered,

point of care tests reduce perioperative transfusions as well as intraoperative blood loss, but they do not have a statistically significant effect on mortality and duration of intensive care.

VEM, also used in cases such as sepsis, has been proven in several systemic reviews, demonstrating increased severity and mortality, especially in hypocoagulation situations. It can also show the hypercoagulation state that occurs after hours or days after trauma or surgery. Platelet and enzymatic hypercoagulation can also be distinguished by new parameters derived from the VEM curve.

Platelet function monitoring

Platelets are necessary as well as functional fibrinogen in clot formation and stability. When vascular endothelium is injured, formation of thrombin is required in order to maintain hemostasis. In cases where vascular endothelin is intact, it is also necessary for the inhibition of thrombus formation. Therefore platelet function is a condition that must be assessed rapidly and essential with fibrinogen for hemostatic clot formation. Platelet function tests are also useful in monitoring hereditary platelet function abnormalities and antiplatelet medications, but are ineffective in demonstrating bleeding or acquired hemorrhagic syndromes [30].

Thrombocytopenia can be obtained simply by complete blood count and can be easily corrected by platelet transfusion. However, platelet function cannot be measured by standard laboratory tests. Platelet activity can be affected by antithrombotic drugs, as well as in many medical conditions, such as in traumatic brain injury or intracranial hemorrhage. Many point of care tests can show us platelet activity. Light transmission aggregometry, platelet-rich plasma is used and is the gold standard for evaluation of platelet activation. However, the complexity of the device and the long-term outcome time limits the use of some central laboratories outside the laboratories. TEG platelet mapping is a modification of TEG and platelet activation in platelets can be assessed by initiating platelet aggregation with the addition of arachidonic acid or adenosine diphosphate to the sample blood [31].

The platelet function analyzer (PFA-100) (Siemens Diagnostics, Deerfield, Ill., USA) uses citrated whole blood passing through disposable cartridges and obtains reliable and reproducible results. PFA-100 has sensitivity for von Willebrand disease screening and presentation of moderate-to-severe platelet abnormality but it is insufficient to demonstrate the effects of antiplatelet agents [19]. Verify Now (Accumetrics, San Diego, CA, USA) tests are available for aspirin, thienopyridines, and glycoprotein IIb / IIIa antagonists and can be used preoperatively to assess risk of bleeding.

PFA-100 was not sufficient fort the assessment of postoperative blood loss in patients undergoing cardiovascular surgery. In addition, research in patients receiving clopidogrel has also been in the background of evaluating blood loss in patients and in the management of blood transfusion. However, evaluation of platelet function also has high specificity.

The Cone and Plate (let) analyzer is effective in screening primer hemostatic disorders such as von Willebrand with accumulation of platelets from whole blood on the artificial surface [32]. Platelet Works is a point of care device that provides an electronic impedance-based cell count used in platelet count and aggregation [33].

Whole blood aggregometry is a commercially available platelet aggregometer that can overcome above the inadequacy of conventional tests by screen filtration pressure method [34]. This device displays platelet aggregation by measuring whole-blood resistance while the whole blood passes through the microelectrode after platelet activation has taken place.

Multiple electrode platelet aggregometry using Whole-blood Impedance Aggregometry (Multiplate) may show risky patients in terms of postoperative platelet transfusion. Despite showing platelet dysfunction by light transmission agregometry and Multiplate, there is no correlation with postoperative blood loss. Multiplate can be used especially for monitoring the effect of antiplatelet drugs [35].

Assessment of platelet activation by point of care tests can determine the amount of antiplatelet agent's effects. In addition, patients, unresponsive to the antiplatelet agents, are provided with normal platelet activity in this tests [36].

Thrombine formation tests

Thrombin measurement was described by Macfarlane and Biggs in 1953 [37]. It was possible to develop a calibrated automatic thrombogram in comparison with a known thrombin activity by further development. Thrombin formation tests are based on fluorogenic or chromogenic principles.

Thrombin formation is a consequence of prothrombin activation and thrombin inactivation [38]. There is a close relationship between the amount of thrombin formed and the tendency to bleeding or thrombotic events.

Calibrated automatic thrombinography (thrombogram) is one of the measurement methods used in the formation of thrombin [39]. In blood coagulation studies, thrombogram is an old and established measuring device. Platelet-poor plasma may show deficiencies of other clotting factors, except FXIII, even in patients using anticoagulants. In platelet-rich plasma, thrombogenesis can elicit the effects of platelets.

Compared with viscoelastic tests, they give better total hemostatic capacity. This provides more information on bleeding monitoring. However, as the platelet rich / poor plasma environment must be created, there is no place for rapid diagnosis.

However, even an experienced laboratory employee obtained the results by running for more than 1 hour. Because of that this test did not find a universal application area.

Limitations in point of care tests

TEG needs daily calibration. Two or three times a day calibration is recommended. Although it can be used with simple laboratory training, TEG should not be used by untrained individuals. TEG needs standardization as a point of care test. Although the required information is obtained in 10 minutes, the whole test requires 30-60 min. For this reason, it is not faster than standard tests.

Viscoelastic coagulation tests evaluate the coagulation state in a static (non-current) state (not an endothelium blood vessel) in cuvette [2]. For this reason, the clinical situation must be considered in evaluating these results in vitro. Although viscoelastic POC tests may show excessive bleeding after cardiopulmonary bypass, efficacy of predicting bleeding is still controversial. Definition of the thrombosis with these devices is time-consuming and does not have a standardization for extended clinical use [37].

TEG and ROTEM ensure that results are obtained 370C and are therefore missing in the prediction of coagulation disorders in hypothermic patients [17]. Point-of-care tests are less precise, with more variation in results. In general, research on price-performance is lacking.

Conclusion

Routine plasma-based tests may also be inadequate to demonstrate coagulopathic bleeding. Point of care tests play an important role in optimizing treatment by ensuring correct product delivery at the right time in the presence of clinical bleeding. They are also effective in the rapid assessment of bleeding especially intraoperatively and can also measure all coagulation parameters in a compact machine at bedside in many areas of medicine. TEG and thromboelastometry are still an important and rapidly developing part of the medicine. POC tests can be used to monitor the treatment of anticoagulants, hyper- and hypocoagulation, and reduce the use of blood products accurately and cheaply.

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