Simulation in coagulation testing using rotational thromboelastometry: A fast emerging, reliable point of care technique

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ABSTRACT

Computer simulations can come in handy to train medical personnel with necessary skills to face the clinical scenarios involving various coagulopathies. Now a days, point of care (POC) devices such as thromboelastography, Sonoclot analyzer and newly approved rotational thromboelastometry (ROTEM) with faster results to assess coagulopathies are available on bedside of patients. ROTEM is emerging as a quick, portable, and well-validated device to evaluate coagulopathy in critical care and perioperative setup. A novel platelet-aggregometry integrated module enables simultaneous analysis of platelets as well as coagulation tests on the same screen. The entire gamut of POC signature curves obtained with different coagulation defects can be learned with graphical simulations. These simulations can be a valuable strategy to elucidate latent conditions, for which simulation interventions can then be designed to mimic different clinical scenarios.

Key words: Coagulation; Graphical simulation; Platelet-aggregometry; Reagents; Rotational thromboelastometry; Thromboelastometer-graphs

INTRODUCTION

The use of computer simulation in medical field has increased the quality of training and safety in terms of patient care. These simulators can come in handy to train medical personnel with necessary skills to face the clinical scenarios involving various coagulopathies. Coagulopathy in critically ill and in patients undergoing major surgery is a concerned cause of morbidity and mortality. The management of these patients was earlier guided by conventional laboratory coagulations tests such as platelet count, prothrombin time, activated partial thromboplastin time, and serum fibrinogen levels.[¹,²] The lengthy turnaround time of these lab tests was a cause of undue delay and improper treatment.[³] Now a days, point of care (POC) devices such as thromboelastography (TEG), Sonoclot analyzer, and newly Food and Drug Administration approved rotational thromboelastometry (ROTEM) with faster results to assess coagulopathies are available on bedside of patients. These viscoelastic POC devices are used to measure the time until clot formation, the dynamics of clot formation, and the stability of clots over time.[⁴,⁵]

The entire gamut of POC signature curves obtained with different coagulation defects can be learned with graphical simulations. These simulations can be a valuable strategy to elucidate latent conditions, for which simulation interventions can then be designed to mimic different clinical scenarios.

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ROTATIONAL THROMBOELASTOMETER

ROTEM is an advancement of TEG and differs in the way of analyzing the coagulation process: In the TEG, the cup is slowly oscillated and changes in viscoelasticity are measured by a pin attached to a suspended torsion wire; whereas, in ROTEM, the cup remains fixed while the pin is oscillated. Moreover, the improved design of ROTEM allows it to be used as a portable device at bedside of the patient. The TEG device has the limitation of inability to distinguish hypofibrinogenemia from thrombocytopenia. However, ROTEM is more suitable as fibrin-specific clot formation (FIBTEM) can be analyzed by inhibiting platelet-fibrinogen interaction using cytochalasin D.

The ROTEM device has four independent analyzer channels which enable the simultaneous independent tests of all parameters [Figure 1]. The various tests of ROTEM are available by use of different activated reagents [Table 1]. These different tests are used simultaneously to derive various ROTEM variables through thromboelastometer graph [Figure 2]. The graphical plot of the clot amplitude versus time displayed on the ROTEM screen is called a “TEMogram” [Figure 3]. The onset of clot is represented by clot time while the rate of fibrin polymerization is represented by clot formation time (CFT) and alpha angle. The maximum clot strength can be judged by maximum clot firmness; whereas, premature lysis or hyperfibrinolysis can be diagnosed by lysis index [Table 2]. In a multicenter study,[7] ROTEM thromboelastometry was shown to yield consistent reference values of these variables among various centers [Table 3].

ROTATIONAL THROMBOELASTOMETRY AND HAEMOSTATIC MANAGEMENT

The rotational thromboelastometry has been used for successfully for POC management in various clinical settings.[8,9] Weber et al. revealed that the hemostatic management based on POC devices (ROTEM) can reduce the patient exposure to blood products and provides significant benefits with respect to clinical outcomes in cardiac surgery patients.[10] Similarly, Fayed et al. observed that ROTEM can predict preoperative transfusion requirements in adult living donor transplant recipients, which may allow better preparation and less cross-matching before surgery.[11]
The ROTEM parameters have been compared and correlated with conventional laboratory coagulation tests. Ogawa et al. conducted a prospective observational study to compare different ROTEM parameters with standard coagulation tests in elective cardiac surgery patients. The author observed strong correlations between FIBTEM-amplitude at 10 min (A10) and fibrinogen level ($r = 0.87; P < 0.001$) and between EXTEM/INTEM-A10 variables and platelet count ($r = 0.72$ and 0.67, respectively; $P < 0.001$). Receiver operating characteristic analysis demonstrated that EXTEM-A10 and INTEM-A10 are predictive of thrombocytopenia below 80 $\times$ 10$^9$/L (area under the curve [AUC], 0.83 and 0.82, respectively), and FIBTEM-A10 was highly predictive of fibrinogen level below 200 mg/dl (AUC, 0.96).[13]

**ROTATIONAL THROMBOELASTOMETRY AND POSTOPERATIVE BLEEDING PREDICTABILITY**

The diagnostic ability of ROTEM to predict postoperative bleeding is a matter of controversy. Reinhofer et al. studied the value of ROTEM to monitor disturbed hemostasis and bleeding risk in patients with cardiopulmonary bypass. The author observed that the positive predictive value and specificity of ROTEM variables such as CFT (71%, 94%) and FIBTEM (73%, 95%) to predict postoperative bleeding was significantly higher than conventional laboratory tests such as aPTT (56%, 72%) and prothrombin time (43%, 5%).[14]

Contrary to this, Davidson et al. observed that ROTEM thromboelastometry has poor positive predictive value (14.8%) to identify patients who bleed more than 200 mL/h in the early postoperative period after cardiac surgery. However, its negative predictive value

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**Table 1: Various rotational thromboelastometry tests with different reagents**

| ROTEM tests | Reagents used | Description |
|-------------|--------------|-------------|
| EXTEM       | Tissue factor activator | Coagulation is activated by small amount of tissue factor to monitor coagulation via extrinsic pathway |
| INTEM       | Ellagic-acid/phospholipid activator | Coagulation is activated by contact phase to monitor coagulation via intrinsic pathway |
| HEPTEM      | Heparinase in combination with INTEM | Comparison of HEPTEM with INTEM parameters can help in detection of heparin-related coagulation disturbances |
| FIBTEM      | Cytochalasin D in combination with EXTEM | Coagulation is activated as in EXTEM after neglecting platelet contribution to the clot firmness |
| APTEM       | Aprotinin, fibrinolysis inhibitor in combination with EXTEM | Coagulation is activated as in EXTEM to monitor the clot firmness after blocking hyperfibrinolysis by aprotinin |
| ECATEM      | Ecarin (prothrombin activator) | Diagnose direct thrombin inhibitor |
| NATEM       | Activated by recalcification only | Sensitive to detect endogenous activators like tissue factor expression on monocytes cells in sepsis, extracorporeal device use, cirrhosis |

**Table 2: Rotational thromboelastometry variables derived from thromboelstometer graph**

| ROTEM variable | Description |
|----------------|-------------|
| CT: Clotting time (s) | Time until the recognizable start of clot formation (2 mm amplitude) |
| CFT: Clot formation time (s) | Time until amplitude of 20 mm is reached. Represents the clot formation dynamics |
| Angle: Alpha-angle (°) | Angle between central line and a tangent to the curve through the 2 mm amplitude point. Represents the kinetics of clot formation |
| MCF: Maximum clot firmness (mm) | Maximum firmness (amplitude) that the clot achieves during the measurement |
| A10-A30: Amplitude at 10-30 min after CT (mm) | Describes the clot firmness at 10-30 min after CT |
| CL30: Clot lysis index at 30 min after CT (%) | Ratio between the MCF and the amplitude 30-60 min after CT. Describes the progress of fibrinolysis |
| ML: Maximal clot lysis (%) | Ratio of the lowest amplitude detected after achieving MCF to the MCF |

**Table 3: The reference values of thromboelastometer variables with different rotational thromboelastometry tests in a multicentre study[7]**

|                | CT (s) | CFT (s) | MCF (mm) | A10 (mm) | CL 30 (%) | ML (%) |
|----------------|--------|---------|----------|----------|-----------|--------|
| INTEM          | 137-246| 40-100  | 52-72    | 44-68    | 94-100    | 0-12   |
| EXTEM          | 42-74  | 46-148  | 49-71    | 43-65    | 95-100    | 0-18   |
| FIBTEM         | 43-69  | -       | 9-25     | 9-24     | -         | -      |

CT: Clot time, CFT: Clot formation time, MCF: Maximum clot firmness, A10: Amplitude 10 min after CT, CL30: Clot lysis index 30 min after CT, ML: Maximal clot lysis
was found to be good (100%). The authors realized that their study was not adequately powered to confirm its poor positive predictive value as the prevalence of bleeding in the early postoperative period was small (13.7%).

**ROTATIONAL THROMBOELASTOMETRY VERSUS OTHER POINT OF CARE DEVICES**

The results of ROTEM analysis have significant less inter- and intra-operator variability as compared to TEG results. Hence, ROTEM is more suitable for use at multiple places as compared to TEG. Recently, a study has compared ROTEM, TEG and Sonoclot analyzer in small number of patients undergoing adult cardiac surgery. The authors observed significant correlations between plasma fibrinogen levels, platelet counts, and variables from the three instruments. They concluded that TEG and ROTEM could be used to detect changes in hemostasis following cardiac surgery. However, Sonoclot seems to be less suitable to detect such changes.

**ROTATIONAL THROMBOELASTOMETRY PLATELET ASSAYS**

The effect of various antiplatelet medications can be studied in ROTEM by integrating a novel aggregometry module in ROTEM system. The various platelet assays can be performed with the use of different activators based on impedance aggregometry. This enables simultaneous analysis of platelet-aggregometry as well as coagulation tests on the same screen.

**CONCLUSION**

ROTEM is emerging as a quick, portable, and well-validated device to assess coagulopathy in critical care and perioperative setup. The routine use of this bedside device can help in timely, hemostatic management of patients prone to bleeding. The designing of computer simulation, mimicking various coagulopathies can prepare the health-care providers to manage hemostasis in the clinical set-up. This POC management can guide the proper usage of coagulation products and reduce the unnecessary blood transfusion and morbidity associated with bleeding and transfusion.

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**CONFLICTS OF INTEREST**

There are no conflicts of interest.

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