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REVIEW ARTICLE

Viscoelastic methods in clinical laboratory hematology: a narrative review

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Abstract

Viscoelastic methods (VEMs) such as thromboelastography (TEG) and thromboelastometry (TEM) offer a comprehensive assessment of hemostasis, starting with early stages of coagulation, through fibrin clot formation, and ending with fibrinolysis.

They offer several advantages compared to the standard coagulation tests i.e. they allow a detailed assessment in real time of the coagulation process with the contribution of platelets and fibrinogen levels in the whole blood. TEG or TEM point-of-care devices are widely used in managing intraoperative bleeding, especially in the context of cardiac surgery. The latest study results indicate a growing interest in VEMs in various fields of hematology. TEG and TEM have been used in congenital bleeding disorders such as hemophilia and von Willebrand disease. Both assays offer more objective and complete laboratory evaluation of an individual patient's phenotype, effective personalized prophylaxis, the management of bypassing agent therapy, and the management of spontaneous bleeding episodes or surgery.

We have therefore carried out a narrative review to summarize evidence on the usefulness of VEMs in the assessment of blood coagulation and fibrinolysis in these bleeding disorders.

Key words: viscoelastic methods (VEMs), thromboelastography (TEG), thromboelastometry (TEM), hemophilia, von Willebrand disease

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Introduction

Viscoelastic methods (VEMs) have been widely developed in recent decades, although the first mention of thromboelastography was made much earlier, in 1948 [1]. Since then, many investigations have been made to optimize and improve this technique, which has become a useful tool for extensive, bedside evaluation of whole blood clotting in real time. VEMs are based on the physicochemical and rheological properties of blood, in that it becomes less viscous and more elastic as it begins to clot [2].

Principles of viscoelastic methods

There are two major and equally important viscoelastic assays: thromboelastography (TEG) and thromboelastometry [TEM and rotational thromboelastometry (ROTEM)]. The principle of the methods is the same for both TEG and ROTEM. A blood sample is transferred to the cup together with appropriate reagents and a pin is placed in the cup. The major difference between these viscoelastic devices concerns the element that rotates. TEG instruments use a fixed pin and oscillating cup (4°45' every 5 s), while ROTEM uses a rotating pin (4°75' every

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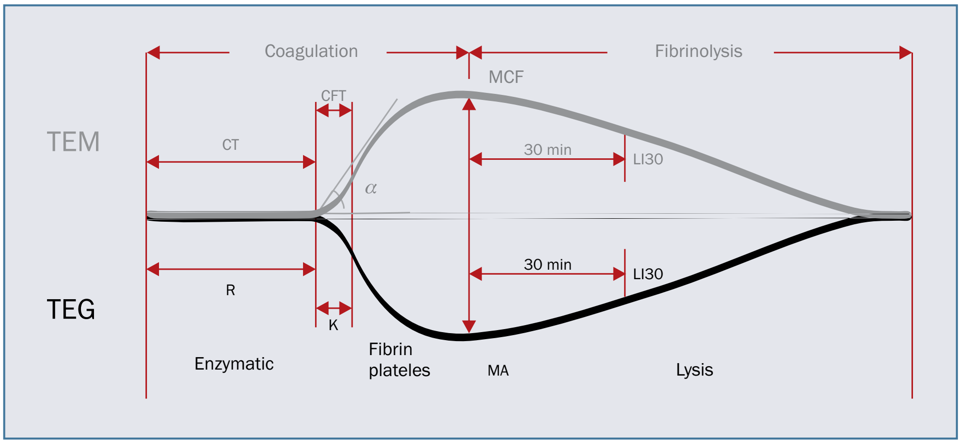

Figure 1. Comparative analysis of thromboelastography (TEG) and thromboelastometry [TEM and rotational thromboelastometry (ROTEM)] tracing and accompanying parameters; CT (clotting time) — period from start of analysis until start of clot formation (until a 2 mm amplitude occurs); CFT (clot formation time) — period until an amplitude of 20 mm is reached (represents clot formation dynamics); MCF (maximum clot firmness) — maximum amplitude of TEMogram; R-time (reaction time) — time to initial fibrin formation; K-time (kinetics time) — time to clot formation; a (alpha angle) — rate of clot formation; MA (maximum amplitude) — absolute clot strength; LI30 (LY30) — fibrinolytic activity 30 minutes after maximum amplitude

6 s) and a stationary cup [3]. There are several activators of blood coagulation that are used in each device to get a detailed evaluation of clot formation, its strength as well as the rate and efficiency of fibrinolysis, such as phospholipid and ellagic acid, tissue factor (TF), TF with cytochalasin D (platelet-independent measurement), and TF with aprotinin or tranexamic acid. Both instruments offer a series of variables as test results, such as clotting time (CT), maximal clot firmness (MCF), clot formation time (CFT), the alpha angle (α) or maximum lysis (ML), although the most characteristic feature of both methods is the graphical presentation of hemostatic processes (Figure 1) [4]. Although TEG and ROTEM traces look similar, the variables are not directly interchangeable and should be interpreted with caution.

TEG and TEM have several advantages compared to standard coagulation tests. They allow for a real-time assessment of the coagulation process with the contribution of platelets number and fibrinogen levels. The absence of one piece of a 'hemostatic jigsaw' is almost immediately visible on the chart. For this reason, both assays enable differential diagnosis of coagulopathy due to thrombocytopenia and coagulopathy due to a- or hypofibrinogenemia. Furthermore, TEG and TEM tests, if carried out for long enough, provide detailed information on the fibrinolytic activity that falls outside the scope of routine tests [4]. Due to its many advantages, viscoelastic methods are used to diagnose coagulopathies, monitor hemostatic treatment, and guide transfusions, primarily in the field of cardiac surgery [5–7].

Role of TEG and TEM in laboratory diagnostics of congenital bleeding disorders

Hemophilia A

Hemophilia A is the most common X-linked recessive congenital bleeding disorder. An absence or severe deficiency of coagulation factor VIII, which is critical for sufficient activation of the coagulation cascade, manifests as spontaneous hemorrhage and abnormal bleeding. Routine coagulation test i.e. activated partial thromboplastin time (aPTT) and factor VIII activity assay are useful in making the diagnosis and severity grading of hemophilia patients. However, standard laboratory tests have only limited use in the monitoring of routine FVIII prophylaxis, as well as the clinical response to different forms of therapy, especially bypassing agents such as recombinant activated factor VII (rFVIIa) and activated prothrombin complex concentrate (aPCC). At this point, viscoelastic methods have proved to be of great utility. Tran et al. have shown a great potential of ROTEM to assess the effectiveness of bypassing agents in hemophilia patients with inhibitors [8]. These results are consistent with the research by Chen et al. who also found that TEG is more sensitive to FVIII inhibitors than other global hemostatic tests [9]. Pivalizza and Escobar [10] used TEG and ROTEM devices to monitor hemostasis during emergency surgery. Both devices have guided large doses of rFVIIa, which were used pre- and intraoperatively. Furukawa et al. [11] also demonstrated that ROTEM tests are helpful in the estimation of appropriate doses of bypassing agents. A comprehensive review by Ramiz et al.

demonstrated that viscoelastic methods could be useful in the management of patients with inhibitors and perioperative management [12]. However, the authors underscore the need for better reproducibility and sensitivity, which are currently operator-dependent.

Furthermore, TEG and ROTEM have been used to monitor the effect of novel therapeutics such as a bispecific antibody to factor IXa (during phase I of clinical studies), or emicizumab that requires more than just standard coagulation tests, to measure response efficacy [12–14]. Yada et al. used ROTEM to monitor patients with hemophilia A taking emicizumab for three consecutive years. The data suggested that ROTEM facilitates assessment of global coagulation in these patients [15].

Von Willebrand disease

Von Willebrand disease (vWD) is a hereditary hemorrhagic disorder which can lead to severe complications due to prolonged mucosal bleeding, bleeding from the gums, epistaxis, easy bruising and heavy menstrual bleeding. Laboratory diagnostics of vWD disease is difficult and time-consuming. Regling et al. [16] have shown that TEG parameters are sensitive in detecting patients with VWF:RCo below 30 IU/dL. Contrary to other laboratory tests, e.g. VWF:RCo, TEG results are performed within an hour and significantly improve the diagnostic process. Moreover, the recent study by Topf et al. [17] showed that new modifications of the standard ROTEM test make it possible to diagnose critical vWD cases. Furthermore, the authors recommend including a ROTEM assay in the current management algorithm of acute microvascular bleeding, especially in severe von Willebrand disease patients [17].

TEG and TEM in laboratory hematology — application perspectives

There are many fields of application of VEMs, especially relating to their use in cardiac surgery or in sepsis [5–8, 18, 19]. These methods could be of great importance in the clinical management of patients with bleeding disorders. In addition, during coronavirus disease 2019 (COVID-19), many studies have demonstrated the indiscriminate utility of TEG and TEM in assessing hemostatic imbalance in the course of this new disease [20–22], showing that both these laboratory techniques indicate hypercoagulability and fibrinolysis shutdown in severe forms of COVID-19, despite the use of thromboprophylaxis [20–22]. Further research should be done on the use of VEMs in both laboratory hematology and COVID-19.

Author’s contributions

JB and EKD performed literature search and wrote the manuscript. AS designed Figure 1. AS and EŻ developed the concept of the manuscript, supervised, and critically read the manuscript. All the authors contributed to the review of the manuscript, and all authors read and approved the final manuscript.

Conflict of interest

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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