Should we integrate viscoelastic assays with standard coagulation screening?

Nathan Visweshwar ,[1] Michael Jaglal,[2] Ankita Patel,[2] Damian Laber,[2] Lubomir Sokol[3]

[1]Department of Hematology, University of South Florida, Tampa, Florida, USA
[2]Department of Hematology/Oncology, Tampa General Hospital, Tampa, Florida, USA
[3]Department of Malignant Hematology, Moffitt Cancer Center, Tampa, Florida, USA

Correspondence to
Dr Nathan Visweshwar, University of South Florida, Tampa, FL 33620, USA; nviswesh@health.usf.edu

Received 7 September 2020
Revised 5 October 2020
Accepted 7 October 2020
Published Online First 12 January 2021

Check for updates

© Author(s) (or their employer(s)) 2021. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Visweshwar N, Jaglal M, Patel A, *et al*. *J Clin Pathol* 2021;**74**:141–143.

SHOULD WE INTEGRATE VISCOELASTIC ASSAYS WITH STANDARD COAGULATION SCREENING?

The standard coagulation screening tests are useful to evaluate but do not give comprehensive assessment of haemostasis. These tests are based on the classification of coagulation systems into distinct extrinsic and intrinsic pathways—assessed by prothrombin time (PT) and activated partial thromboplastin time (APTT), respectively. However, the current evidence suggests that tissue factor activates the coagulation cascade, converting factor VII to VIIa—which in turn activates factor X and the intrinsic pathway via factor IX.[1] Standard coagulation screening takes between 27 min and 77 min and these tests were not developed to predict bleeding or guide treatment.[2] In an emergency, this delay may be crucial—hindering the clinicians with their decision-making process.

A detailed personal (surgery, dental extraction) and family history is the ideal initial screening for excluding a haemostatic disorder prior to the interventional and surgical procedures. However, in an emergency when the history is not available, it is difficult to assess the patient's proneness for bleeding. Even when the coagulation screening test results are available, there are pitfalls in interpretation. When PT and APTT are within the normal range, it is assumed that the coagulation factors are above 30%, and that postprocedural bleeding should not be a major concern.[3] However, a normal coagulation screen does not reflect a patient's risk of bleeding during interventional procedures.[4] Furthermore, abnormally prolonged APTT does not directly correlate with the severity of bleeding, and the replacement therapy may lead to the increased risk of thrombosis.[5] The fibrinolytic system is not assessed by standard coagulation screening. Acquired hyperfibrinolysis is observed in a variety of clinical scenarios including liver transplantation, cardiac surgery, vascular surgery, postpartum haemorrhage, cancer and severe trauma.[6] Factors playing a major role in in vivo haemostasis including stasis of blood, activation of the endothelium, activation of the innate immunity (involving monocytes, neutrophils and platelets), activation of platelets, concentration and nature of microparticles are not assessed by the standard coagulation assays. The validity of coagulation screening is now being questioned.[7]

Viscoelastic assays provide a global measure of the functional aspect of haemostasis in real time. These assays analyse clot strength using the maximum amplitude and length (figure 1).[8] The three viscoelastic assays presently available include: thromboelastography (TEG), rotational thromboelastogram (ROTEM) and Sonoclot analyzer to assess coagulation, platelet function and fibrinolysis. The new generation of viscoelastic assays also incorporate platelet function tests, resulting in a significant reduction of surgical re-exploration rate and help with appropriate utilisation of fresh frozen plasma and platelet concentrates. Thromboelastogram clot strength using the maximum amplitude cut-off of 40 mm is predictive of major obstetric haemorrhage (95% CI).[9] However, a single postoperative viscoelastic assay may not be useful for prediction of bleeding. If abnormalities of viscoelastic parameters are seen on repeat testing, the patient should be closely monitored for bleeding and intervention with appropriate blood components considered. A randomised trial comparing TEG to standard coagulation tests demonstrated a statistically significant reduction in fibrinogen monitoring in liver transplantation.[10] The platelet count in patients with cirrhosis cannot be used to predict the risk of bleeding, because thrombin generation may be increased as platelets in cirrhosis may be hyperactive.[11] In clinical practice, platelets infused before invasive procedures may not significantly increase the platelet count or improve haemostasis in patients with cirrhosis, but TEG tracing may help with proper use of blood products.

Viscoelastic assays help with better utilisation of blood products which improves the clinical outcome. When compared with standard coagulation assays, the TEG-guided approach reduces the use of allogeneic blood components by about 58% compared with the standard coagulation tests.[12] Rotational thromboelastometry significantly reduces blood loss and decreases requirements for Packed Red Blood Cells (PRBCs) (30.8 vs 62.3%; $p<0.001$) and Fresh Frozen Plasma (FFP) (25.0 vs 56.5%; $p<0.001$) during cardiac surgery.[13] A randomised controlled trial using rapid-TEG in the management of trauma reported a significant reduction in the utilisation of blood products and a decrease in death rate at 28 days with viscoelastic assays. In this trial, 20 deaths with standard coagulation tests (36.4%) versus 11 with viscoelastic assays (19.6%) were observed. The number of haemorrhagic deaths was lower with viscoelastic assays compared with standard coagulation screening (8.9% vs 20%).[14] A systematic review by Whiting *et al* [15] concluded that viscoelastic assays are more cost-effective in the utilisation of blood products and management of haemostasis than standard laboratory.

J Clin Pathol: first published as 10.1136/jclinpath-2020-207099 on 12 January 2021. Downloaded from http://jcp.bmj.com/ on March 11, 2021 at Seoul National University Medical Library and Hospital. Protected by copyright.

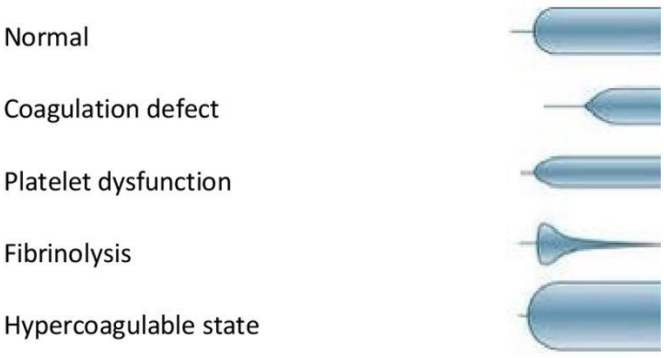

Figure 1 Thromboelastography tracings.

Standard coagulation screening lacks the ability to assess bleeding and fails to identify hypercoagulable states. The viscoelastic assays identify hypercoagulable state despite negative thrombophilia screening in 38% of individuals.[16] The inherited defects of thrombophilia account for only 10% of patients with venous thromboembolism. About 25%–50% of patients presenting with their first episode of Venous THrombo Embolosm (VTE) have no clear risk factors—inherited or acquired.[17] The annual incidence of spontaneous thromboembolic events in carriers of *antithrombin*, protein C, S and Factor V Leiden mutation was 0.40% and 0.11%, respectively, when compared with 0.1% in non-carriers.[18] In the thromboelastogram on patients undergoing abdominal surgery, the maximum amplitude of the TEG was predictive of venous thromboembilism with a sensitivity of 72% and a specificity of 69%, in patients not treated with prophylactic heparin.[19] Among patients treated with thrombopoietin receptor agonists for management of thrombocytopenia undergoing interventional procedures in cirrhosis, only patients with hypercoagulable states developed thrombotic events.[20] However, viscoelastic assays cannot be used as the sole screening method in patients referred for thrombophilia workup, as it fails to identify 43% of patients with underlying hypercoagulable states.[16]

Viscoelastic assays require quality control measures before incorporating them into routine clinical practice. Precision of viscoelastic assays varies widely. The methodology checks, the internal quality control of the user, the device and the reagents vary between centres. The coefficient of variation of individual tests is between 7.4% and 19% for TEG and 2.6% and 11.2% for ROTEM. The precision of the tests in the UK external quality assurance programme varied with the coefficients of variances ranging from 7.1% to 39.9% for TEG and 7.0% to 83.6% for ROTEM.[21] However, modern viscoelastic assays are reliable and have increased precision and reproducibility with 100% negative predictive value for bleeding in some cases.[22] So far, there is no evidence that TEG or ROTEM improve morbidity or mortality in patients with severe bleeding. This is not because of lack of precision or validation of testing, but results from clinicians' interpretation of viscoelastic test results and consequent treatment decisions.[23]

The guidelines from the European Society of Anaesthesiology suggest the use of viscoelastic assays during liver transplant for management of haemostasis. The UK National Institute for Health and Care Excellence recommends use of ROTEM and TEG to monitor clotting during and after cardiac surgery but not for management of obstetric or trauma-induced bleeding.[6] The Food and Drug Administration (FDA) and European Medicines Agency granted marketing authorisation for the point-of-care thromboelastogram device for assessing coagulation. However, viscoelastic assays lack the quality-assurance methodologies required by regulatory agencies such as the American Association of Blood Banks, FDA and College of American Pathologists. Currently, the routine use of viscoelastometric point-of-care testing (ROTEM, TEG and Sonoclot systems) is not a standard practice, but with better quality control measures, this may change. As haematologists, we hope all the tools needed for a comprehensive assessment of haemostasis will be available for better patient care in the near future.

Handling editor Mary Frances McMullin.

Acknowledgements The authors thank Beth Schachter, PhD for assistance in reviewing this manuscript.

Contributors All the authors have contributed equally in writing this manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests NV has been on advisory board at Biogen Idec. MJ has been on advisory board/speaker's bureau at Novartis.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD
Nathan Visweshwar http://orcid.org/0000-0002-3995-4018

REFERENCES

1 Rapaport SI, Rao LVM. The tissue factor pathway: how it has become a "prima ballerina". *Thromb Haemost* 1995;74:007–17.
2 Yuan S, Ferrell C, Chandler WL. Comparing the prothrombin time Inr versus the APTT to evaluate the coagulopathy of acute trauma. *Thromb Res* 2007;120:29–37.
3 Teruya J, Oropeza M, Ramsey G. A normal aPTT does not guarantee adequate coagulation factor levels. *Anesthesiology* 2001;94:542.
4 Segal JB, Dzik WH, Transfusion Medicine/Hemostasis Clinical Trials Network. Paucity of studies to support that abnormal coagulation test results predict bleeding in the setting of invasive procedures: an evidence-based review. *Transfusion* 2005;45:1413–25.
5 Duga S, Salomon O. *Congenital factor XI deficiency: an update. paper presented at: seminars in thrombosis and hemostasis*, 2013.
6 Newland A, Kroese M, Akehurst R, *et al*. *Nice diagnostics guidance 13: detecting, managing and monitoring haemostasis: viscoelastometric point-of-care testing (ROTEM, TEG and Sonoclot systems)*. National Institute for Health and Care Excellence (NICE), 2014.
7 Mannucci PM. Abnormal hemostasis tests and bleeding in chronic liver disease: are they related? no. *J Thromb Haemost* 2006;4:721–3.
8 Abuelkasem E, Lu S, Tanaka K, *et al*. Comparison between thrombelastography and thromboelastometry in hyperfibrinolysis detection during adult liver transplantation. *Br J Anaesth* 2016;116:507–12.
9 Barinov SV, Zhukovsky YG, Dolgikh VT, *et al*. Novel combined strategy of obstetric haemorrhage management during caesarean section using intrauterine balloon tamponade. *J Matern Fetal Neonatal Med* 2017;30:29–33.
10 Wang S-C, Shieh J-F, Chang K-Y, *et al*. *Thromboelastography-guided transfusion decreases intraoperative blood transfusion during orthotopic liver transplantation: randomized clinical trial. paper presented at: transplantation proceedings*, 2010.
11 Pihusch R, Rank A, Göhring P, *et al*. Platelet function rather than plasmatic coagulation explains hypercoagulable state in cholestatic liver disease. *J Hepatol* 2002;37:548–55.
12 Westbrook AJ, Olsen J, Bailey M, *et al*. Protocol based on thromboelastograph (TEG) out-performs physician preference using laboratory coagulation tests to guide blood replacement during and after cardiac surgery: a pilot study. *Heart Lung Circ* 2009;18:277–88.
13 Ichikawa J, Marubuchi T, Nishiyama K, *et al*. Introduction of thromboelastometry-guided administration of fresh-frozen plasma is associated with decreased allogeneic blood transfusions and post-operative blood loss in cardiopulmonary-bypass surgery. *Blood Transfus* 2018;16:244.
14 Gonzalez E, Moore EE, Moore HB, *et al*. Goal-Directed hemostatic resuscitation of trauma-induced coagulopathy: a pragmatic randomized clinical trial comparing a viscoelastic assay to conventional coagulation assays. *Ann Surg* 2016;263:1051.
15 Whiting P, Al M, Westwood M. Viscoelastic point-of-care testing to assist with the diagnosis. *management and monitoring of haemostasis: a systematic review and cost-effectiveness analysis* 2015.
16 O'Donnell J, Riddell A, Owens D, *et al*. Role of the Thrombelastograph as an adjunctive test in thrombophilia screening. *Blood Coagul Fibrinolysis* 2004;15:207–11.

J Clin Pathol: first published as 10.1136/jclinpath-2020-207099 on 12 January 2021. Downloaded from http://jcp.bmj.com/ on March 11, 2021 at Seoul National University Medical Library and Hospital. Protected by copyright.

17 White RH. The epidemiology of venous thromboembolism. *Circulation* 2003;107:4I-–8.
18 Middeldorp S, Henkens CM, Koopman MM, *et al*. The incidence of venous thromboembolism in family members of patients with factor V Leiden mutation and venous thrombosis. *Ann Intern Med* 1998;128:15–20.
19 Traverso C, Arcelus J, Gomez E, *et al*. Prospective assessment of the risk of deep vein thrombosis in elective abdominal surgery. predictive role of thromboelastography. *Thrombotic and haemorrhagic disorders* 1993;7:9–15.
20 Afdhal NH, Giannini EG, Tayyab G, *et al*. Eltrombopag before procedures in patients with cirrhosis and thrombocytopenia. *N Engl J Med* 2012;367:716–24.
21 Kitchen DP, Kitchen S, Jennings I, *et al*. *Quality assurance and quality control of thrombelastography and rotational Thromboelastometry: the UK NEQAS for blood coagulation experience. paper presented at: seminars in thrombosis and hemostasis*, 2010.
22 Vig S, Chitolie A, Bevan DH, *et al*. Thromboelastography: a reliable test? *Blood Coagul Fibrinolysis* 2001;12:555–61.
23 Whiting P, Al M, Westwood M, *et al*. Viscoelastic point-of-care testing to assist with the diagnosis, management and monitoring of haemostasis: a systematic review and cost-effectiveness analysis. *Health Technol Assess* 2015;19:1–228.

J Clin Pathol: first published as 10.1136/jclinpath-2020-207099 on 12 January 2021. Downloaded from http://jcp.bmj.com/ on March 11, 2021 at Seoul National University Medical Library and Hospital. Protected by copyright.