The use of viscoelastic haemostatic assays in non-cardiac surgical settings: a systematic review and meta-analysis

Raimondo De Cristofaro

Institute of Internal Medicine and Geriatrics, Haemostasis and Thrombosis Centre, Fondazione Policlinico Universitario "Agostino Gemelli", Area of Haematological Sciences, Catholic University of the Sacred Heart School of Medicine, Rome, Italy

Considerable efforts have been made over the past decades to develop rapid and efficient tests capable of guiding transfusion therapies during surgical procedures and severe trauma burdened by heavy blood loss. Viscoelastic haemostatic assays (VHA), including rotational thromboelastometry (ROTEM®, Penthapharm, Basel, Switzerland) and thromboelastography (TEG®, Hemoscope-Hemonetics, Niles, IL, USA) are rapid, whole blood assays that can determine clot viscoelastic strength upon coagulation activation by standardised reagents[1]. With these methods, clotting and fibrinolysis can be studied in whole blood and, therefore, the contribution of platelets and other blood cells to the different phases of coagulation activation can be investigated, together with the formation and propagation of coagulum and its dissolution by fibrinolytic enzymes. These phenomena cannot be investigated separately by common coagulation tests such as prothrombin time (PT) or activated partial thromboplastin time (APTT). In a clinical setting, VHAs also have the crucial advantage of speed, and can act as point of care (POC) tests during surgery associated with major bleeding, including cardiothoracic surgery, liver transplantation, and severe trauma. The goal of VHA testing is to optimise transfusion regimes of red cells/platelets, clotting factors, fibrinogen, fresh frozen plasma or cryoprecipitate, and administration of antifibrinolytic drugs. This approach is aimed at improving clinical outcomes and reducing costs[2]. VHAs have found wide applications in cardiothoracic surgery and liver transplantation, whereas their use in other surgical settings has been minimal[3]. The meta-analysis by Franchini *et al.* in this issue of *Blood Transfusion*[4] reviewed studies on the use of VHAs in non-cardiac surgery. Franchini *et al.*[4] have carried out a systematic and rigorous review and meta-analysis of four randomised controlled trials (RCTs) involving the use and outcomes of VHAs in non-cardiac surgery (liver transplantation, surgery in bleeding burn patients, trauma-induced coagulopathy, and invasive procedures in patients with severe coagulopathy associated with liver cirrhosis)[4].

One of the most important problems of VHAs stems from the lack of standardised and validated methods to activate coagulation in blood samples[1]. The physical nature of the viscoelastic methods has meant that, despite their versatility, adoption of these assays outside the management of massive bleeding has been slow. Different degrees of coagulation activation in a blood sample may be obtained depending on the biochemical nature and concentration of the activating agent (kaolin, ellacid acid, synthetic or natural phospholipids, recombinant tissue factor, calcium concentration, etc.)[1]. Moreover, observed alterations of the viscoelastographic traces may depend on the perturbed contribution of single coagulation factors, fibrinogen, platelets, red blood cells or drugs[5]. Thus, the operator has to use different cartridges to identify the factor responsible for the observed abnormality from both TEG® or ROTEM®. For example, if we need to verify whether an alteration in maximum clot firmness (MCF) for the ROTEM® and maximal amplitude (MA) for the TEG® is to be attributed to thrombocytopenia or hypofibrinogenaemia, we have to abolish the platelet contribution to MCF/MA with abciximab (a functional fibrinogen assay), cytochalasin D (FIBTEM® assay), or a combination of cytochalasin D and tirofiban (FIBTEM plus®) to identify singularly the contribution of fibrinogen to clot firmness[6]. Several studies have also remarked on the role played by red blood cells in the dynamics of clot formation of whole blood in VHAs. For example, anaemia was found to be associated with reduced clot formation times (CFT) and increased alpha-angle (α-angle), and MCF in the ROTEM® assay[7]. This cannot be explained by defects in conventional plasma coagulation assays or platelet aggregation tests[8]. The effects of anaemia are also associated with an increase in MCF obtained with the ROTEM FIBTEM® reagent. Thus, another clinical feature that should be considered in the analysis of VHA results is the haematocrit level in blood samples, a factor that is sometimes not taken into consideration by the operator. Another unsolved issue concerns the intra- and inter-assay reproducibility of VHAs. Unfortunately, there is no suitable whole blood control material that allows assessment across different centres. The coefficient of variation in ROTEM® parameters in citrated whole blood ranges from 2 to 14% in a study performed in six centres[9]; this differs from the lower CV (approx. 5%) of conventional laboratory assays. This discrepancy may be

*Blood Transfus 2018; **16**: 224-6* DOI 10.2450/2018.0040-18

due to the above-mentioned issues concerning the type and concentration of activator, the use of citrated blood as opposed to whole blood, or the time elapsed between sampling and processing. Additional variability may also be due to the use of VHAs as a POC approach, even amongst trained individuals[10]. On the other hand, VHA methods, especially ROTEM, are undoubtedly useful in some clinical settings. Fast and reliable assessment of plasma fibrinogen concentration is, indeed, of particular interest, since plasma fibrinogen concentration and MCF in FIBTEM® assays have been demonstrated to have a good predictive value for perioperative bleeding complications and need for massive transfusion in trauma, orthopaedic surgery, postpartum haemorrhage, and cardiac surgery[11-14]. Furthermore, FIBTEM®-guided administration of fibrinogen concentrate was shown to be associated with reduced transfusion requirements in patients after severe trauma or undergoing major surgery without any increase in the incidence of thromboembolic events[15-18]. Moreover, FIBTEM® provides not only an alternative assessment for plasma fibrinogen concentration, but also gives additional information on fibrinogen polymerisation defects due to dysfibrinogenaemia, both inherited or, more often, present in liver cirrhosis or colloid infusion[19]. In addition, hydroxyethyl starch solutions can erroneously provide high fibrinogen concentration measurements yielded by coagulation analysers using optical methods[20]. Thus, assessing FIBTEM® MCF seems to be preferable to monitoring fibrin polymerisation in patients treated with infusion of colloids, such as hydroxyethyl starch solutions. Another issue that demands careful attention is the fibrinolysis phase, especially in patients undergoing liver transplantation. Here, VHAs may have a big advantage since they can rapidly identify gross fibrinolysis abnormalities during the late phases of the surgical procedure, allowing a specific therapy for hyperfibrinolysis, which is responsible for excessive bleeding, to be initiated.

Considering all the above-mentioned "*pros*" and "*cons*" of VHA methodology, the meta-analysis by Franchini *et al.*[4] has the merit of showing that the use of VHA does not offer a significant and tangible benefit in terms of mortality rates and transfusion needs compared to standard monitoring in patients undergoing non-cardiac surgery. This has been achieved within the limits of the low quality of evidence resulting from the inherent risk of bias, imprecision and inconsistency in the data available. Thus, future RCTs must be well-designed and eliminate any confounding factors in order to show whether or not VHAs can replace conventional coagulations assays and optimise important primary end points such as mortality and transfusion needs in non-cardiac surgery. In the meantime, the choice between guiding transfusion therapies with VHAs or with conventional laboratory tests during non-cardiac surgical procedures can be based on the organisation of laboratory services within the hospital (for shipping samples, carrying out tests, and reporting results), which may or may not guarantee a quick and efficient response to requests for coagulation tests. Further considerations about the economic cost of VHAs in comparison with conventional coagulation assays should only be made once their clinical convenience has been demonstrated. Thus, larger and well-designed RCTs, as proposed by Franchini *et al.*[4], should be carried out in this area to better clarify the exact role of VHAs in the management of these acquired bleeding conditions.

The Author declares no conflict of interest.

References

1) Wikkelso A, Wettersley J, Moller AM, Afshari A. Thromboelastography (TEG) or rotational thromboelastometry (ROTEM) to monitor haemostatic treatment in bleeding patients: a systematic review with meta-analysis and trial sequential analysis. Anaesthesia 2016; **72**: 519-31.
2) Hans GA, Besser MW. The place of viscoelastic testing in clinical practice. Br J Haematol 2016; **173**: 37-48.
3) Serraino GF, Murphy GJ. Routine use of viscoelastic blood tests for diagnosis and treatment of coagulopathic bleeding in cardiac surgery: updated systematic review and meta-analysis. Br J Anaesth 2017; **118**: 823-33.
4) Franchini M, Mengoli C, Cruciani M, et al. The use of viscoelastic hemostatic assays in non-cardiac surgical setting: a systematic review and meta-analysis. Blood Transfus 2018; **16**: 235-43.
5) Nogami K. The utility of thromboelastography in inherited and acquired bleeding disorders. Br J Haematol 2016; **174**: 503-14.
6) Solomon C, Schochl H, Ranucci M, et al. Comparison of fibrin-based clot elasticity parameters measured by free oscillation rheometry (ReoRox (R)) versus thromboelastometry (ROTEM (R)). Scand J Clin Lab Invest 2015; **75**: 239-46.
7) Spiezia L, Radu C, Marchioro P, et al. Peculiar whole blood rotation thromboelastometry (Rotem) profile in 40 sideropenic anaemia patients. Thromb Haemost 2008; **100**: 1106-10.
8) Solomon C, Rahe-Meyer N, Schochl H, et al. Effect of haematocrit on fibrin-based clot firmness in the FIBTEM test. Blood Transfus 2012; **11**: 412-8.
9) Lang T, Bauters A, Braun SL, et al. Multi-centre investigation on reference ranges for ROTEM thromboelastometry. Blood Coagul Fibrinolysis 2005; **16**: 301-10.
10) Hagemo JS, Naess PA, Johansson P, et al. Evaluation of TEG((R)) and RoTEM((R)) inter-changeability in trauma patients. Injury 2013; **44**: 600-5.
11) Carling MS, Jeppsson A, Wessberg P, et al. Preoperative fibrinogen plasma concentration is associated with perioperative bleeding and transfusion requirements in scoliosis surgery. Spine 2011; **36**: 549-55.
12) Charbit B, Mandelbrot L, Samain E, et al. The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage. J Thromb Haemost 2007; **5**: 266-73.
13) Karlsson M, Ternstrom L, Hyllner M, et al. Plasma fibrinogen level, bleeding, and transfusion after on-pump coronary artery bypass grafting surgery: a prospective observational study. Transfusion 2008; **48**: 2152-8.

14) Reinhofer M, Brauer M, Franke U, et al. The value of rotation thromboelastometry to monitor disturbed perioperative haemostasis and bleeding risk in patients with cardiopulmonary bypass. Blood Coagul Fibrinolysis 2008; **19**: 212-9.
15) Schochl H, Nienaber U, Hofer G, et al. Goal-directed coagulation management of major trauma patients using thromboelastometry (ROTEM)-guided administration of fibrinogen concentrate and prothrombin complex concentrate. Crit Care 2010; **14**: R55.
16) Nienaber U, Innerhofer P, Westermann I, et al. The impact of fresh frozen plasma vs coagulation factor concentrates on morbidity and mortality in trauma-associated haemorrhage and massive transfusion. Injury 2011; **42**: 697-701.
17) Weber CF, Gorlinger K, Meininger D, et al. Point-of-care testing: a prospective, randomized clinical trial of efficacy in coagulopathic cardiac surgery patients. Anesthesiology 2012; **117**: 531-47.
18) Fenger-Eriksen C, Jensen TM, Kristensen BS, et al. Fibrinogen substitution improves whole blood clot firmness after dilution with hydroxyethyl starch in bleeding patients undergoing radical cystectomy: a randomized, placebo-controlled clinical trial. J Thromb Haemost 2009; **7**: 795-802.
19) Bolliger D, Gorlinger K, Tanaka KA. Pathophysiology and treatment of coagulopathy in massive hemorrhage and hemodilution. Anesthesiology 2010; **113**: 1205-19.
20) Fenger-Eriksen C, Moore GW, Rangarajan S, et al. Fibrinogen estimates are influenced by methods of measurement and hemodilution with colloid plasma expanders. Transfusion 2010; **50**: 2571-6.

Correspondence: Raimondo De Cristofaro
Institute of Internal Medicine and Geriatrics, Haemostasis and Thrombosis Centre, Fondazione Policlinico Universitario "Agostino Gemelli"
Area of Haematological Sciences, Catholic University of the Sacred Heart School of Medicine
Largo Francesco Vito 1
00168 Rome, Italy
e-mail: raimondo.decristofaro@unicatt.it