VISCOELASTIC TESTING IN PATIENT BLOOD MANAGEMENT: FRIEND OR FOE?

By Mark T. Friedman, DO
NYU Langone Health
NYU Grossman Long Island School of Medicine
Mineola, NY

Viscoelastic tests (VETs) represent an advancement in hemostasis assessment compared with conventional coagulation tests (CCTs) such as activated partial thromboplastin time (aPTT), prothrombin time (PT), thrombin time (TT), etc. in that they assess whole blood (WB) hemostasis rather than just plasma coagulation factor clot initiation.

Although VETs are not a recent technology, having been first developed in the 1940s, their use has only become more prevalent in the past 20-25 years. Much of this interest in VETs has been driven not only by the urgency to deliver improved care during hemorrhagic emergencies, such as trauma care and postpartum hemorrhage, but also by the uptake in the implementation of patient blood management (PBM) programs with intent to assess hemostasis in real time and reduce unnecessary blood product use in clinical settings such as cardiothoracic surgery and liver transplantation.

Yet, there is potential for misuse or overuse of VETs due to poor clinical training and experience in using the technology along with lack of standardization for their use, which may lead to overordering and misinterpretation of VETs resulting in inappropriate blood product use.[1,2]

UNDERSTANDING VETS

To understand VETs, one must understand the technology behind these devices. Traditional thromboelastography (TEG) and rotational thromboelastometry (ROTEM) platforms employed a pin and cup mechanism in which patient citrated WB in a cup rotated relative to a pin (TEG 5000, Haemonetics) or vice versa (ROTEM delta, Werfenand) the gradual change of WB from its liquid form to solid clot and clot breakdown (lysis) was measured and translated into a tracing. The weaknesses in this design include that much sample pipetting was necessary and that the devices were subject to vibration artifact (i.e., if the devices were errantly disturbed during the sample run), limiting their application as a point-of-care test (POCT). Upgrades to the devices included cartridge-based clot detection via resonance at a fixed vibration frequency range (TEG 6s) and automated sample draw into the cartridge testing chambers containing all reagents (TEG 6s and ROTEM sigma). Although ROTEM has retained the rotating pin system in its newer device, both newer-generation devices offer more flexibility for use as POCTs due to reduced pipetting and smaller sample volume, though vibration artifact has not been entirely eliminated.[3,4] Another

system recently made available has introduced clot detection through ultrasound, known as sonorrheomtery (sonic estimation of elasticity via resonance [SEER], Quantra, HemoSonics, LLC) which similarly uses a cartridge-based testing platform and requires no pipetting.[5] Please note, this list of VET analyzers is not exhaustive as other devices, such as the ClotPro system (Haemonetics), are approved outside of the United States.[6]

Although a VET-guided transfusion strategy could reduce blood product usage, as concluded by a 2016 Cochrane Review, the results from this study were primarily based upon low level evidence from trials of elective cardiac surgery involving cardiopulmonary bypass.[7] In a follow up study, the Viscoelastic Haemostatic Assay Augmented Protocols for Major Trauma Haemorrhage (ITACTIC) Trial, a pragmatic, European multicenter randomized controlled trial conducted from 2016 to 2018, assigned participating trauma centers to implement either VET-guided (TEG or ROTEM) or CCT-guided transfusion protocols as a core study requirement.[8] Eligibility criteria were based on clinical suspicion of major trauma hemorrhage, and while not all enrolled patients ultimately received massive transfusion protocols (MTPs) within 24 hours, all were managed according to the transfusion strategy to which their institution had been randomized. This design ensured that the transfusion approach (VET vs. CCT) was systematically applied across institutions, permitting protocol-level comparisons. The study investigators found no significant outcome difference (i.e., alive and free of massive transfusion) at 24 hours (primary outcome) between the two groups, nor was there any difference in secondary outcomes (including mortality at 28 days, median time to hemostasis, patients with symptomatic thromboembolism and median hospital length-of-stay [LOS], among others). The study, however, did find a significantly reduced 28-day mortality in the VET arm (44% vs. 74%; $p = 0.02$) in subgroup analysis of patients with severe traumatic brain injury. Nevertheless, there were significant limitations to this study, including that only a small proportion of patients in both arms received MTPs at 24 hours (26% and 28% in the VET vs. the CCT group, respectively).

CLINICAL USES OF VETS

Studies of VET use in cardiothoracic surgery have positively shown reductions in allogeneic blood product transfusions, yet, have not consistently shown to improve outcomes (including mortality, stroke, prolonged intubation, emergency reoperation for bleeding, or ICU and hospital LOS).[9,10,11,12] A recent literature review and expert opinion proposed a TEG 6s algorithm for use in cardiac surgery, although the algorithm was based on limited evidence.[12] The authors concluded that while further research is needed to validate the use of a TEG 6s algorithm, clinicians could continue to rely on older established TEG 5000 (pin and cup)-based algorithms based on observed correlation between the two devices.

Postpartum hemorrhage (PPH) continues to be a leading cause of maternal mortality, accounting for nearly a third of all maternal deaths globally.[13] Although observational data reported significant reductions in blood product use in cases of severe PPH (defined as blood loss in excess of 1500 cc) associated with VET-guided management, a small, single center randomized controlled trial did not find evidence to support that and there is conflicting evidence about the effectiveness of ROTEM-guided algorithms in PPH management.[14]

Liver transplantation (LT) is often complicated by coagulopathy associated with end-stage liver disease (ESLD). ESLD coagulopathy involves both reduced procoagulant and anticoagulant (i.e., protein C, protein S, and antithrombin) factors, a state known as rebalanced hemostasis, inadequately reflected by hypocoagulable prolonged CCT results (i.e., aPTT and PT) since both bleeding and thrombosis may occur.[15,16] Aside from low levels of coagulation factors, issues contributing to bleeding in LT include surgical technique, anatomical variations, ESLD severity, ischemia-reperfusion injury in new liver grafts, renal impairment, dysfibrinogenemia and thrombocytopenia.[15,16] Prothrombotic changes in ESLD in addition to reduced natural anticoagulant factors include elevated levels of von Willebrand factor (VWF) and factor VIII, as well as reduced ADAMTS-13 levels. Portal hypertension and low levels of fibrinolytic components (i.e., alpha-2-antiplasmin and plasminogen) may also contribute to bleeding or thrombosis in ESLD.[15,16]
Use of VETs in LT dates back to the first human orthotopic LT performed in 1963.[17,18] Evidence-based VET algorithms (both TEG and ROTEM) have since been published to aid in reducing excessive transfusion associated with prolonged CCTs which has resulted in fewer postoperative complications, including lower rates of reoperation for bleeding, retransplantation, acute kidney injury, and overall hemodynamic instability.[15,17] Yet, hospital LOS and overall survival have not been conclusively impacted by the use of VETs versus CCTs in LT, and it has been reported that VETs may underestimate the coagulation capacity of ESLD due in part to insensitivity to measurement of the endothelial contribution via thrombomodulin protein C activation and VWF platelet adhesion.[15,17]

Finally, VETs have also been found to be useful in providing a more comprehensive assessment of coagulopathy in patients with COVID-19-related pneumonia and in identifying patients with COVID-19 who manifest with more severe symptoms owing to inflammatory mechanisms that can trigger a cytokine storm leading to hypercoagulability and thrombotic risk.[19,20]

In conclusion, VETs offer an advancement in hemostasis assessment with more rapid turnaround time and ability to assess total clot strength and fibrinolysis, but they are more costly to run than CCTs, require more expertise when interpreting results, and lack standardization.[1] While there is published data demonstrating benefits of VETs for PBM in select clinical settings, there is still much more to study, including its use in the pediatric population.

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