2014 Consensus conference on viscoelastic test–based transfusion guidelines for early trauma resuscitation: Report of the panel

Kenji Inaba, MD, Sandro Rizoli, MD, Precilla V. Veigas, MSc, Jeannie Callum, MD, Ross Davenport, MD, John Hess, MD, Marc Maegele, MD,
and **the Viscoelastic Testing in Trauma Consensus Panel,*** *Los Angeles, California*

ABSTRACT: There has been an increased interest in the use of viscoelastic testing to guide blood product replacement during the acute resuscitation of the injured patient. Currently, no uniformly accepted guidelines exist for how this technology should be integrated into clinical care. In September 2014, an international multidisciplinary group of leaders in the field of trauma coagulopathy and resuscitation was assembled for a 2-day consensus conference in Philadelphia, Pennsylvania. This panel included trauma surgeons, hematologists, blood bank specialists, anesthesiologists, and the lay public.

Nine questions regarding the impact of viscoelastic testing in the early resuscitation of trauma patients were developed before the conference by panel consensus. *Early use* was defined as baseline viscoelastic test result thresholds obtained within the first minutes of hospital arrival—when conventional laboratory results are not available. The available data for each question were then reviewed in person using standardized presentations by the expert panel. A consensus summary document was then developed and reviewed by the panel in an open forum. Finally, a two-round Delphi poll was administered to the panel of experts regarding viscoelastic thresholds for triggering the initiation of specific treatments including fibrinogen, platelets, plasma, and prothrombin complex concentrates. This report summarizes the findings and recommendations of this consensus conference. (*J Trauma Acute Care Surg*. 2015;78: 1220–1229. Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.)

KEY WORDS: Consensus conference; guidelines; viscoelastic testing; early resuscitation; trauma.

Despite all of the major advances in resuscitation science that have been integrated into contemporary trauma care, hemorrhage remains the leading cause of preventable death after injury.[1–3] Because of this, the primary focus of any management strategy for an injured patient is the recognition, control, and mitigation of acute blood loss. One of the key components of this is the correction of any systemic coagulation defects, a problem that is common even at admission,[4–7] with the potential to become even more pronounced across time. Although, currently, the correction of coagulation defects in the most severely bleeding patient is often achieved with empirical use of fixed ratios of complementary blood products, in ideal circumstances, hemostatic interventions targeting specific defects, guided by laboratory testing, would be preferable.

Current laboratory assays have limitations that restrict their usefulness in guiding the early resuscitation of injured patients who are actively bleeding. A promising alternative, viscoelastic testing, uses whole blood and provides both dynamic and timely information through measurement of clot formation and dissolution across time that can be performed as a point-of-care whole-blood test. Originally described by Hartert[8,9]

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From the Division of Trauma and Surgical Critical Care (K.I.), University of Southern California, Los Angeles, California; Departments of Surgery and Critical Care Medicine, St. Michael's Hospital, and University of Toronto (S.R.); Department of Surgery, Sunnybrook Health Sciences Center and Institute of Medical Science, University of Toronto (P.V.); and Department of Clinical Pathology, Sunnybrook Health Sciences Center Toronto, and Department of Laboratory Medicine and Pathobiology, University of Toronto (J.C.), Toronto, Ontario, Canada; Centre for Trauma Sciences, Blizard Institute, Bart's and the London School of Medicine and Dentistry, Queen Mary University of London (R.D.), London, United Kingdom; Department of Laboratory Medicine (J.H.), School of Medicine, University of Washington, Seattle, Washington; and Department of Traumatology and Orthopedic Surgery (M.M.), Institute for Research in Operative Medicine (IFOM), Private University Witten/Herdecke Ostmerheimserstr, Köln, Germany.

*Viscoelastic Testing in Trauma Expert Panel: Daniel Bolliger, MD, University of Basel Hospital, Basel, Switzerland; Karim Brohi, MD, Centre for Trauma Sciences, Queen Mary University of London, UK; Andrew Cap, MD, PhD, US Army Institute of Surgical Research, Ft. Sam Houston, Texas, United States; Michael P Chapman, MD, University of Colorado-Denver, Colorado, United States; Mitchell Jay Cohen, MD, School of Medicine, University of California, San Francisco, United States; Bryan A Cotton, MD, University of Texas Health Science Center at Houston, United States; Nicola Curry, MD, Oxford Haemophilia & Thrombosis Centre, University of Oxford, Oxford, UK; Fries, Dietmar, MD, Medical University Innsbruck, Austria; Frith, Daniel, MD, PhD, Centre for Trauma Sciences, Queen Mary University of London, UK; Görlinger, Klaus, MD, University Hospital of Essen, Germany and TEM International GmbH, Munich, Germany; Haas, Thorsten, MD, University Children's Hospital Zurich, Switzerland; Karkouti, Kayvan, MD, Toronto General Hospital, University Health Network, Toronto, Canada; Martini, Wenjun, PhD, US Army Institute of Surgical Research, Ft. Sam Houston, Texas, United States; Nascimento, Bartolomeu, MD, Sunnybrook Health Sciences Center, Toronto, ON, Canada; Scarpelini, Sandro, MD, Faculty of Medicine of Ribeiro Preto, University of São Paulo, Brazil; Schöchl, Herbert, MD, AUVA Trauma Center Salzburg, Austria; Schreiber, Martin, MD, Oregon Health & Sciences University, Oregon, United States; Theusinger, Oliver, MD, University Hospital Zurich, Zurich, Switzerland.

Address for reprints: Kenji Inaba, MD, Division of Trauma and Surgical Critical Care, University of Southern California, LAC + USC Medical Center, 2051 Marengo St IPT, C5L100 Los Angeles, CA 90033; email: kenji.inaba@med.usc.edu.

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in 1948, two commercially available products dominate the current market. The first is the TEG 5000 (Haemonetics Corporation, Braintree, MA), which is used predominantly in the United States, and the other is ROTEM (TEM International GmbH, Munich, Germany), which has a large presence in Europe and Canada. Both of these devices use a pin suspended in a cup of recalcified or native whole blood. As the pin and cup rotate relative to each other with repetitive, controlled, low shear movements, the formation and eventual dissolution of clot are captured as changes in torque, which are then transduced into a visual tracing. Although the mechanical principles underlying the two tests are similar, the different hardware and activators result in different output values (Table 1) and reference ranges, with results that cannot be used interchangeably. These principles and reference ranges have been extensively reviewed.[10–12]

Despite its long history, the use of this technology in trauma care has only recently generated widespread interest. Despite the growing evidence base supporting its use, many facets of its integration into clinical care remain unclear and no universally accepted guidelines for its use exist. While this is also true for conventional laboratory test–based markers of coagulopathy,[13–16] with the rapidly expanding literature base on viscoelastic testing, and the potential that this technology could change resuscitation practices, a consensus conference was organized. In September 2014, an international group of leaders in the field of trauma coagulopathy and resuscitation was assembled for a 2-day consensus conference in Philadelphia, Pennsylvania. This multidisciplinary panel included trauma surgeons, hematologists, blood bank specialists, anesthesiologists, and the lay public. Nine specific questions regarding the role of viscoelastic testing in trauma patients were developed before the conference by panel consensus and posted for public review. Each of these questions was then reviewed in person using standardized presentations of the relevant evidence by the expert panel. The evidence focused on the early use of viscoelastic testing in civilian adult trauma. *Early use* was defined as baseline viscoelastic test result thresholds obtained within the first minutes of hospital arrival—when conventional laboratory results are not available. At the conclusion of the presentations, a consensus summary document was developed and reviewed by the panel in an open forum. The conference was held just before a large international trauma meeting and was open to all members and the general public.

At the conclusion of the consensus conference, a two-round Delphi poll was administered to the panel of experts regarding the use of viscoelastic thresholds for triggering the initiation of specific treatments including fibrinogen, platelets, plasma, and prothrombin complex concentrates (PCCs). The Delphi method is a structured interactive communication technique coordinated by a facilitator. The panel of experts answered a set of questions in a preset number of rounds, with an anonymous summary of the results being presented to the expert panel after each round. The experts were encouraged to revise their answers in light of the responses from the other panel members. Responses were collected and analyzed, and conflicting viewpoints were identified. During this process, the range of answers narrows and the group progresses toward a consensus. The results of the Delphi poll will be presented under each appropriate category.

The purpose of this consensus conference was to develop a set of viscoelastic test–based thresholds (Fig. 1; Table 2) that would indicate the need for hemostatic interventions during the acute early phase of resuscitation based on current evidence and expert practice. High-value areas to be targeted for future research were also discussed (Table 3). The specific goals of the conference were to do the following:

1. Summarize and consolidate the existing evidence on optimal viscoelastic test threshold values used to diagnose coagulopathy, guide hemostatic interventions including blood product transfusion, and predict mortality in injured patients.
2. Present institutional experience regarding the use of viscoelastic testing.
3. Develop guidelines for the early resuscitation of trauma patients based on the viscoelastic test threshold values.

QUESTION 1. IS THERE A VISCOELASTIC TEST PARAMETER THRESHOLD THAT CAN PREDICT MORTALITY OR THE NEED FOR A MASSIVE TRANSFUSION IN TRAUMA PATIENTS?

Question 1a. Mortality

The acute coagulopathy of trauma as diagnosed by conventional laboratory testing has been associated with a significant increase in mortality.[5,7] Viscoelastic testing in these patients produces a signature trace of traumatic coagulopathy[17] and is also associated with increased mortality. However, like with conventional testing, strict threshold cutoff values remain elusive as the available data have been generated through the testing of arbitrary thresholds rather than rigorous cut-point analyses. In a prospective analysis of 334 patients evaluated with ROTEM,[18] 24-hour mortality was increased when maximum clot firmness (MCF) FIBTEM of 7 mm or less (21% vs. 9%, $p = 0.006$), clotting time (CT) EXTEM of 100 seconds or longer (45.5% vs. 8.4%, $p < 0.001$), clot formation time (CFT) EXTEM of 200 seconds or longer (27% vs. 8.7%, $p < 0.001$), and MCF EXTEM of 45 mm or less (25.4% vs. 9.4%, $p = 0.001$) were examined. After adjustment for confounding variables, these

TABLE 1. Reference Ranges

ROTEM	CT, s	CFT, s	α Angle, degrees	A10, mm	A20, mm	MCF, mm
INTEM	122–208	45–110	70–81	40–60	51–72	51–72
EXTEM	43–82	48–127	65–80	40–60	50–70	52–70
FIBTEM						7–24
TEG	R, min	K, min	α Angle, degrees	MA, mm	LY30, %	G, dynes/cm^2
	5–10	1–3	53–72	50–70	0–8	4.5–11.0 k

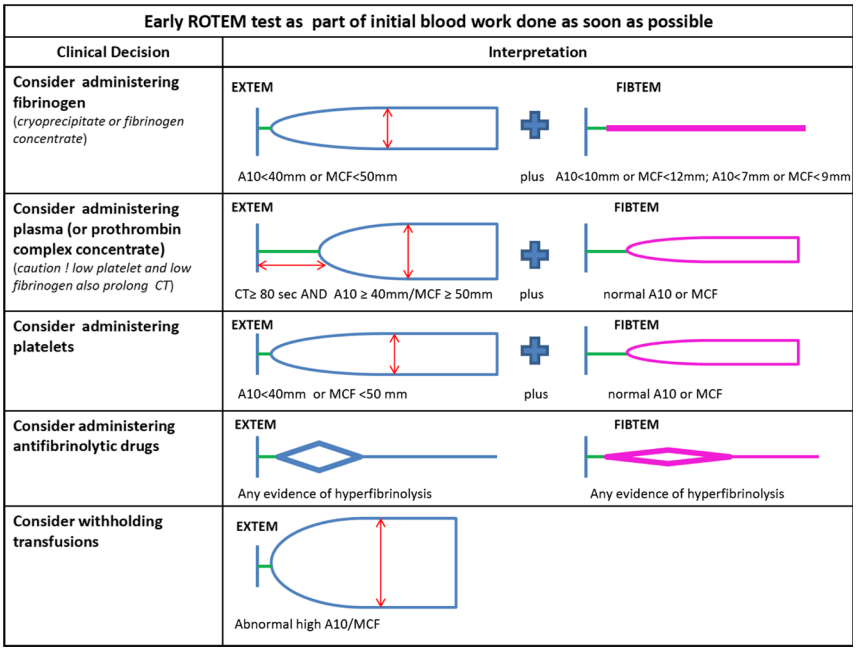

Figure 1. ROTEM algorithm for early trauma resuscitation.

values and LI60 EXTEM were independently associated with death. In patients with isolated traumatic brain injury, MCF FIBTEM had a strong association with mortality.[19] For TEG, retrospective analysis of TEG values on admission demonstrated low clot strength (maximal amplitude [MA] < 50 mm)[20] and derived G,[21] to be independently associated with mortality.

Hyperfibrinolysis[22–24] in particular has been demonstrated by both tests to be tightly associated with mortality. In the work by Schöchl et al.[25] using ROTEM, hyperfibrinolysis (maximum lysis, 100%) was separated into three groups based on the time it was diagnosed (<30 minutes (fulminant), 30–60 minutes (intermediate), and >60 minutes [late]), demonstrating a stepwise increase in mortality from 73% for late, 91% for intermediate, and 100% for fulminant. Theusinger et al.[26] demonstrated that hyperfibrinolysis associated with trauma had a significantly higher mortality than in patients with hyperfibrinolysis from nontrauma causes or matched patients without hyperfibrinolysis. In the study by Tauber et al.,[18] hyperfibrinolysis was associated with a high degree of mortality, especially for those with complete dissolution of the clot within 60 minutes. In a prospective study from France, ROTEM was demonstrated to be highly sensitive and specific for the detection of hyperfibrinolysis, which was associated with a significantly higher mortality (100% vs. 11%, $p < 0.05$).[27] In two studies using admission TEG data from Denver,[24,28] one from Los Angeles[29] and another from Houston,[30] hyperfibrinolysis was demonstrated to be a major predictor of death. In the Denver study,[28] for those requiring a massive

TABLE 2. Key Recommendations

Consideration be given to the use of viscoelastic testing during the early phases of trauma resuscitation.

Although clotting time may detect abnormalities in clot initiation, the current evidence is insufficient to recommend an exact threshold for fresh-frozen plasma or PCC transfusion.

Although the available data are insufficient to support a precise threshold for fibrinogen replacement, the expert recommendation is to consider cryoprecipitate or fibrinogen concentrate transfusion when abnormalities in clot strength are detected on viscoelastic testing.

Viscoelastic testing is highly specific for fibrinolysis and should be used during early trauma resuscitation to identify injured patients with systemic hyperfibrinolysis. Any evidence of hyperfibrinolysis during early resuscitation should warrant consideration of antifibrinolytic medications.

The panel recommends against the use of viscoelastic testing for withholding antifibrinolytic therapy.

Hypercoagulable or normal results during early resuscitation should lead to the consideration of withholding blood product transfusion.

Cost-effectiveness has been demonstrated in the nontrauma setting and is in large part caused by the decrease in the consumption of blood products, which may result from improved hemostatic management.

Normal viscoelastic test results can be seen in patients with mechanical bleeding or significant coagulopathy caused by hypothermia, acidosis, warfarin and other oral anticoagulant medications, von Willebrand's disease, platelet inhibitors and platelet dysfunction.

The optimal location for equipment setup is institution dependent but should allow for rapid testing and communication to the clinical team if it is to be used for the early resuscitation of bleeding trauma patients. Viscoelastic testing can be used as a point-of-care test.

Testing should also meet the local regulations that govern laboratory testing in this location.

The person(s) performing the tests and interpreting the results should be trained and educated adequately.

TABLE 3. Future Research Opportunities

1. Prospective multicenter validation of a viscoelastic test–guided transfusion protocol
2. Validation of reference ranges for injured patients
3. Development and validation of a mechanism for external proficiency testing
4. Modification of the preexisting hardware to improve portability and strength for use under adverse conditions
5. Improvements to specimen processing, sample throughput, and the output of data

transfusion (MT), an LY30 of 3% or greater was associated with substantially higher mortality (45.5% vs. 4.8%, $p = 0.001$). Reduced clot strength and hyperfibrinolysis are strong predictors of mortality in trauma patients and may be used to prognosticate early in the resuscitation of major hemorrhage. Viscoelastic testing is important because conventional coagulation testing is not practical for diagnosing hyperfibrinolysis during the acute resuscitation phase of care. The traditional Euglobin Clot Lysis test is time-consuming and is not available at most centers around the clock. This will be further expanded on in Question 4, which addresses hyperfibrinolysis and its treatment with antifibrinolytic medications.

Question 1b. Massive Transfusion

The ability to predict the need for an MT is clinically relevant, facilitating communication with the Blood Bank and providing lead time for the preparation of blood products. For research study design, this also allows for improved screening for injured patients who will require blood products. The difficulty in answering this question rests with the uncertainty surrounding the optimal definition of what constitutes an MT. Both the volume of blood and the time span across which it is administered are actively being debated. A more pragmatic question may be what viscoelastic test values predict the need for blood product transfusion? The majority of the available data have focused on the MA or MCF as a reflection of clot strength. In a study by Schöchl et al.[31] of 323 patients, using more than 10 units of packed red blood cells (PRBCs) in 24 hours as the definition of an MT, admission FIBTEM A10 and MCF were highly predictive of an MT. Davenport et al.[17] has demonstrated that an EXTEM A5 less than 35 mm could predict the need for an MT faster and more accurately than the international normalized ratio. In the study by Tauber et al.,[18] the MCF FIBTEM was independently associated with the need for early blood transfusion within the first 6 hours.

For TEG, Cotton et al.[32] demonstrated an activated clotting time (ACT) longer than 128 seconds predicted the need for more than 10 PRBCs in the first 6 hours (odds ratio [OR], 5.15; 95% confidence interval [95% CI], 1.36–19.49; $p = 0.01$) and that an ACT less than 105 seconds predicted not needing any transfusion in the first 24 hours (OR, 2.80; 95% CI, 1.02–7.07; $p = 0.04$). In another study from this institution,[33] an alpha angle less than 56 degrees was highly predictive of the need for an MT (OR, 8.99; 95% CI, 2.86–28.29; $p < 0.001$) defined as more than 10 PRBCs every 6 hours. Pezold et al.[21] using the same definition of an MT showed that TEG-derived G as a marker of clot strength was an independent predictor as well. In a recent comparison of ROTEM with TEG,[34] A10 values and FIBTEM MCF seemed to be the best discriminators of the need for an MT.

Recommendation of the Consensus Panel

We recommend that consideration be given to the use of viscoelastic testing during the early phases of trauma resuscitation for the following reasons:

1. There is a strong association between early abnormal results (in particular, clot strength and systemic hyperfibrinolysis) and mortality as well as the need for MT.
2. This is the only practical test capable of diagnosing hyperfibrinolysis with a high degree of specificity within the time constraints of early trauma resuscitation.
3. The time to onset of hyperfibrinolysis, with earlier being worse, and the magnitude of hyperfibrinolysis correlate to increased mortality.

Further considerations such as cost, time, accuracy, and variables affecting results are addressed in Questions 7 and 8.

QUESTION 2. IS THERE A VISCOELASTIC TEST PARAMETER THRESHOLD THAT CAN BE USED TO GUIDE THE ADMINISTRATION OF PLASMA OR PCC?

As a point-of-care whole-blood test, viscoelastic testing would theoretically allow for the rapid evaluation of the coagulation profile of an injured patient, allowing a targeted infusion of specific blood products to correct specific deficits. Plasma and the importance of its early role in the resuscitation of the injured patient have been extensively studied; however, studies using ROTEM or TEG to guide its transfusion are lacking. The available data attempt to retrospectively correlate specific viscoelastic test findings to the "need" for plasma as evaluated by the amount of plasma given to a patient during a fixed time after the test was run. This study design does not allow a direct evaluation of the impact of plasma infusion for a specific viscoelastic test threshold value.

Using TEG, Nystrup et al.[20] demonstrated that low clot strength correlated with an increased transfusion of plasma within the first 24 hours. In a study by Holcomb et al.,[33] all output values except for LY30 predicted plasma transfusion in the first 6 hours. In a study from Denver,[35] maximum rate of thrombin generation more than 9.2 mm/min at 3 hours was associated with a decrease in plasma usage. Not all of the available studies support this association. In a study evaluating 161 injured patients, none of the output values differed between those who did and did not get transfused.[36] ROTEM has also been studied in this manner. Davenport et al.[17] has demonstrated that patients with an EXTEM A5 less than 35 mm were more likely to receive a plasma transfusion (37% vs. 11%, $p < 0.001$).

For PCC, two retrospective studies were available for review. Schöchl et al.[37] examined 131 patients who received fibrinogen concentrate as the initial treatment. Of these, 98 additional patients received PCC when EXTEM CT was prolonged by 1.5 times normal. A blunt comparison of the observed mortality against TRISS (Trauma and Injury Severity Score)-predicted mortality demonstrated favorable outcomes. In a further study, ROTEM-guided PCC transfusion was compared with patients receiving plasma empirically, demonstrating a decrease in exposure to blood products.[38]

Recommendation of the Consensus Panel

While the CT may detect abnormalities in clot initiation, the current evidence is insufficient to recommend an exact threshold for fresh-frozen plasma or PCC transfusion.

The two-round Delphi poll revealed little agreement among the participants when asked about the viscoelastic triggers for the transfusion of plasma or PCC. Of the participant

group, 15 (65%) of 23 would consider transfusion when EXTEM CT was 80 seconds or longer (plus EXTEM A10 ≥ 40 mm or EXTEM MCF ≥ 50 mm). The major concern among the participants was the lack of rigorous data to support this recommendation and the differences between plasma and PCC. Low platelet count and low fibrinogen levels may also prolong EXTEM CT and should be considered in the decision to use this value as a transfusion trigger for plasma or PCC.

QUESTION 3. IS THERE A VISCOELASTIC TEST PARAMETER THRESHOLD THAT CAN BE USED TO GUIDE THE ADMINISTRATION OF FIBRINOGEN CONCENTRATE OR CRYOPRECIPITATE?

Fibrinogen is essential for hemostasis and is one of the first clotting factors to fall to critical values after major traumatic hemorrhage.[39–41] Depressed levels have been associated with poor outcomes including mortality.[22,39–42] There is a lack of consensus on the optimal serum level that would require replacement with trigger values ranging from 0.8 to 2.0 g/dL.[43] The current standard for conventional fibrinogen testing is the Clauss method of fibrinogen measurement. Although it can take upward of 30 to 60 minutes to obtain the result, FIBTEM correlates well with this value.[41,44] In the presence of artificial colloids in particular, the Clauss method may overestimate fibrinogen levels, thus favoring the use of viscoelastic testing.[45] Preclinical animal models demonstrate that ROTEM-guided fibrinogen supplementation in trauma can be effective.[46–48] Clinically, because ROTEM can identify low levels of functional fibrinogen, it can help direct replacement therapy in fibrinogen-depleted states.[46,49] Rugeri et al.[44] has shown that there is good correlation between fibrinogen and FIBTEM A10, with a trigger value of 1 g/dL equal to a cut point of 6 mm. Other groups have used a FIBTEM A10 of less than 7 mm or MCF of less than 7 mm[18] or a FIBTEM MCF of 10 to 12 mm.[37,50] The direct impact on survival of using these thresholds for fibrinogen replacement is not known.

Recommendation of the Consensus Panel

Although the available data are insufficient to support a precise threshold for fibrinogen replacement, the expert recommendation is to consider cryoprecipitate or fibrinogen concentrate transfusion when abnormalities in clot strength are detected on viscoelastic testing.

The two-round Delphi poll revealed agreement among 20 (87%) of 23 participants who would consider the administration of a fibrinogen concentrate or cryoprecipitate in patients with the following viscoelastic testing parameters: FIBTEM A10 of less than 10 mm corresponding to a FIBTEM MCF of less than 12 mm (plus abnormal low EXTEM A10 < 40 mm corresponding to an EXTEM MCF < 50 mm). There was concern expressed by 3 (13%) of 23 participants regarding the threshold. These participants favored a lower treatment threshold of FIBTEM A10 of less than 7mm corresponding to a FIBTEM MCF of less than 9 mm to avoid excessive fibrinogen administration (Fig. 1).

The considerations supporting this recommendation include:

1. Early abnormalities in clot strength on viscoelastic testing correlate with conventional laboratory fibrinogen measurements.
2. Viscoelastic testing results can be more rapidly obtained than conventional Clauss method measurements.
3. Viscoelastic testing can detect functional deficits in fibrin polymerization.

QUESTION 4. IS THERE A VISCOELASTIC TEST PARAMETER THRESHOLD THAT CAN BE USED TO GUIDE THE ADMINISTRATION OF ANTIFIBRINOLYTIC MEDICATIONS?

Fibrinolysis is an integral part of the coagulation process. After injury, excess fibrinolysis has been implicated as an important component of early trauma-induced coagulopathy and, as discussed in Question 1, is tightly associated with mortality. This becomes important because there are pharmacologic antifibrinolytic agents available to mitigate this hyperfibrinolysis, which when tested in a large multinational randomized controlled trial was shown to decrease mortality.[51] Because of the study design and lack of mechanistic coagulation data, however, universally accepted indications for antifibrinolytic administration have not been established and viscoelastic testing in theory may provide guidance. Conventional coagulation testing is not practical for diagnosing hyperfibrinolysis. The euglobulin clot lysis test is not available in most centers at all times of the day and takes 90 minutes of observation before the test is complete. Using viscoelastic testing, however, an estimate of systemic fibrinolysis can be obtained with good correlation to the euglobulin clot lysis values. In the study by Levrat et al.,[27] 87 trauma patients were prospectively studied using both admission ROTEM and euglobulin clot lysis time with hyperfibrinolysis defined at less than 90 minutes. Using threshold values of EXTEM MCF 18 mm, CLI30 71%, and increase of APTEM MCF 7%, a sensitivity of 100%, 75%, and 80%, respectively, with a specificity of 100% was found. In the work done by Raza et al.,[52] the magnitude of fibrinolysis may in fact be greater than that detected by viscoelastic testing when plasmin-antiplasmin complex and D-dimer level analysis is used as the gold standard for measurement. The optimal cutoff for treatment or additional doses of antifibrinolytic medications if required however have not been studied. The original LY30 threshold of 7.5%[30] may be too high. Work done by the group in Denver using TEG[28,53] suggests that at an LY30 of 3% or greater may be a more sensitive cutoff value for the detection of hyperfibrinolysis. To date, however, a validation of the outcomes associated with viscoelastic test–guided antifibrinolytic therapy has not been performed. Likewise, the sensitivity of viscoelastic testing is insufficient to support its use for withholding antifibrinolytic therapy if hyperfibrinolysis is absent.

Recommendation of the Consensus Panel

Viscoelastic testing is highly specific for fibrinolysis and should be used during early trauma resuscitation to identify injured patients with systemic hyperfibrinolysis.

The panel recommends against the use of viscoelastic testing for withholding antifibrinolytic therapy.

While waiting for viscoelastic test results may delay timely antifibrinolytic therapy, the panel recommendation is that any viscoelastic evidence of hyperfibrinolysis during the early resuscitation of a bleeding trauma patient should warrant consideration of antifibrinolytic medication administration if not yet already administered.

The two-round Delphi poll revealed agreement among 21 (91%) of 23 participants who would consider the use of an antifibrinolytic medication in patients where there is viscoelastic evidence of lysis (Fig. 1). Viscoelastic parameters consistent with fibrinolysis include ML of 5% or more within 1 hour (corresponding to an LI60 ≤ 95%), EXTEM A5 less than 35 mm (corresponding to an EXTEM A10 < 45 mm or an EXTEM MCF < 55 mm), or a flat line in FIBTEM (FIBTEM CT > 600 seconds).

QUESTION 5. IS THERE A VISCOELASTIC TEST PARAMETER THRESHOLD THAT CAN BE USED TO GUIDE THE ADMINISTRATION OF PLATELETS?

For the administration of platelets, viscoelastic testing has been correlated to platelet counts that are commonly used as a transfusion trigger (50×10^9/L and/or 100×10^9/L). In a retrospective study of 44 patients where the platelet count was compared with the MA,[54] correlation with a k-value of 0.48 was found. When transfusion thresholds were compared, platelet count less than 100×10^9/L and MA less than 52 mm demonstrated near-identical impact on transfusion decision making. In a study of 90 patients,[44] platelet count was correlated to INTEM A15 ($r = 0.57$) and EXTEM A15 ($r = 0.56$). An INTEM A15 of less than 46 mm correlated well to a platelet count of 50×10^9/L, with a sensitivity of 100% and a specificity of 83%. In another study,[34] platelet count correlated best with INTEM A10 (Spearman's $p = 0.54$) and EXTEM A10 (Spearman's $p = 0.51$). Several reports have published cutoff values for platelet transfusion; however, these are based on expert opinion. ROTEM values of EXTEM A10 less than 40 mm,[55] EXTEM A10 less than 35 to 42 mm,[56] and INTEM A10 less than 40 mm[57] and TEG values of MA less than 45 to 49 mm[56] and MA less than 55 mm[58] have been published. The differing cutoff values tested in these studies and the lack of uniformity in platelet transfusion practices make the determination of a threshold viscoelastic test value unattainable.

Recommendation of the Consensus Panel

The available data do not support an exact threshold for treatment; however, the two-round Delphi poll revealed agreement among 21 (92%) of 23 participants who would consider platelet transfusion in patients where viscoelastic testing demonstrated an abnormally low EXTEM A10 or EXTEM MCF (plus normal FIBTEM A10). It was noted by the participants that this was an indirect measure of platelet function. An abnormality in these measures may be specified as any EXTEM A10 or EXTEM MCF below the reference range (EXTEM A10 < 40 mm corresponding to an EXTEM MCF < 50 mm).

The considerations supporting this recommendation are the following:

1. There is a correlation between clot strength as measured by viscoelastic testing and platelet count.
2. A high fibrinogen level can mask abnormal platelet count or function on clot firmness.

QUESTION 6. IS THERE A VISCOELASTIC TEST PARAMETER THRESHOLD THAT CAN BE USED TO WITHHOLD THE TRANSFUSION OF BLOOD PRODUCTS?

In the acute resuscitation phase of a trauma patient, as long as there is no clinically apparent bleeding, normal viscoelastic test values should allow for the withholding of blood products. There are no studies available to support this; however, the administration of plasma or platelets to a hemodynamically normal patient with no evidence of bleeding and normal ROTEM or TEG values would be difficult to justify. In the study from Houston, an ACT of less than 105 seconds was associated with no need for transfusion in the first 24 hours.[32] For the hypercoagulable patient, the administration of blood products would be contraindicated. The hypercoagulable state can be diagnosed by viscoelastic testing but not by conventional coagulation tests.[59–63] This state can be seen early on admission blood sampling and would preclude the need for any blood product transfusion acutely unless otherwise dictated by the patient's clinical presentation.

Recommendation of the Consensus Panel

While there are no data to support the use of viscoelastic testing results to withhold transfusion, the panel recommendation is that hypercoagulable results during early resuscitation should lead to the consideration of withholding blood product transfusion. There is also evidence that hypercoagulable viscoelastic testing results are associated with a reduced need for hemostatic resuscitation.

QUESTION 7. IS THERE A PRACTICAL ADVANTAGE IN TERMS OF COST, TIME, OR LOGISTICS WHEN VISCOELASTIC TESTING IS COMPARED WITH CONVENTIONAL LABORATORY TESTING?

Question 7a. Cost

Cost data in general are lacking. There are complex factors that need to be considered that include equipment costs, maintenance, training, personnel, sample handling, and data entry, all of which can vary according to the setup of the system within a specific institution. The migration from a standard conventional test–based protocol for the transfusion of components to one using a viscoelastic test–based algorithm in the cardiac surgery literature[64] reduced costs at one institution by $267,658 per year. In a study out of Houston, as emphasized by the authors, cost and charge values vary widely between institutions; however, at this hospital, the charge for a set of conventional laboratory tests was comparable to that for TEG ($286 vs. $317).[33] The National Institute for Health and Care Excellence Diagnostics Assessment Program in the United Kingdom performed an evidence review for viscoelastic testing.[65] They found in their cost-effectiveness

analysis that this test would be cost-effective if more than 80 tests were performed each year.

Question 7b. Time

The time to data output can be critical if viscoelastic testing or any other coagulation parameter is to be effectively integrated into the early phase of resuscitation. This has long been espoused as one of the advantages of viscoelastic testing over conventional coagulation tests, especially if performed as a point-of-care test. When platelets were examined, the median turnaround time for the standard platelet count was 13 minutes (interquartile range [IQR], 9–22 minutes) as compared with 12 minutes for EXTEM A5.[66] In a different study, the conventional test took 16 minutes (SD, 10.3) compared with 63.7 minutes (SD, 19.1) for the full tracing, with preliminary data becoming available at approximately 30 minutes.[67] In this study, a conventional coagulation laboratory panel took 20 minutes (SD, 9.9) as compared with 60 minutes for the full tracing.

For fibrinogen and fibrinolysis, viscoelastic testing however may have a distinct advantage. The turnaround time for Clauss fibrinogen in one study was 37 minutes (IQR, 31–54 minutes) as compared with 12 minutes for FIBTEM A5.[66] In a pediatric study, fibrinogen testing took 53 minutes (IQR, 45–63 minutes), whereas the A10 measurement took only 23 minutes (IQR, 21–24 minutes).[68] Of note, the standard Clauss fibrinogen assay can be modified to provide a more rapid result.[69] For fibrinolysis, TEG and ROTEM remain the only practical tests available in the acute resuscitation phase as the standard euglobulin clot lysis test is not available in most centers at all times and takes 90 minutes of observation before the test is complete.

Question 7c. Accuracy

The quality control process is a major issue for viscoelastic testing especially if it is used in a satellite setting away from the core laboratory as a point-of-care test by a clinical care provider. An external proficiency testing report[70] from the United Kingdom's National External Quality Assessment Scheme raised major concerns regarding the lack of precision of both TEG and ROTEM. Overall, 18 TEG and 10 ROTEM users were sent a total of eight blood samples including both normal and abnormal samples. They found a lack of uniformity in the output values, with coefficients of variance ranging from 7.1% to 39.9% for TEG and 7.0% to 83.6% for ROTEM.[70] The results between centers were so different that if transfusion decisions were made based on these results, the treatments would have differed between centers. There may be differences between the two available technologies. In one study performed in cardiac patients, ROTEM analyses were found to be more reproducible than those found on TEG.[71]

Recommendation of the Consensus Panel

Question 7a. Cost

The costs of starting a program may range from 100,000 to 125,000 USD. Ongoing costs are comparable to those of other conventional coagulation tests.

Cost-effectiveness has been demonstrated in the nontrauma setting and is in large part caused by the decrease in the consumption of blood products, which may result from improved hemostatic management.

Question 7b. Time

There is a time advantage with the use of viscoelastic testing for the measurement of fibrinogen and fibrinolysis and overall screening of hemostatic competence.

Question 7c. Accuracy

Accuracy and reproducibility of viscoelastic testing in the trauma setting requires further study.

QUESTION 8. ARE THERE PATIENT VARIABLES THAT CAN INTERFERE WITH THE INTERPRETATION OF VISCOELASTIC TEST RESULTS?

Patient variables can affect the results obtained from viscoelastic testing. Because viscoelastic tests work by activating plasma coagulation, which in turn recruits platelets with the strong platelet activator thrombin, problems in the normal weak platelet activation pathways may not be detected. Platelet adhesion defects in a high shear situation such as von Willebrand's disease can be missed. Likewise, drug-related coagulopathy caused by aspirin, clopidogrel, or hydroxyethyl starch will also go undetected.[72] However, GPIIb-IIIa inhibitors will be detected. Therefore, in clinical practice, where the coagulopathy is being driven by defects in platelet adhesion or adhesion-coupled activation, the platelet count may be a better marker for thrombocytopenic bleeding. MCF, as measured on ROTEM, has also been demonstrated to correlate with the changes in clot strength caused by anemia.[73,74] Alcohol has also been demonstrated to result in a hypocoagulable state, with decreased fibrin formation, clot strength, and rate of fibrin cross-linking.[75] This may be gender specific, with a positive correlation to alcohol seen in men. The presence of gender differences in normal viscoelastic testing is unclear.[76] For pediatric reference ranges, older than 1 year, minimal differences have been noted with increasing age.[77]

Preanalytic variables include the technique of drawing and the use of anticoagulation.[78–80] Unlike the elective blood draw for conventional testing, which is performed by a trained clinician gently using large-bore silicone-lined needle, sample acquisition and handling in the chaotic trauma bay may result in platelet activation by shear, with subsequent loss of activity and alteration of the test result.[80] This has been demonstrated by testing a sample repeatedly during the first hour after the draw.[79] If a nonanticoagulated sample is used, differences in the time from draw to test will result in variability in the test results.[81] If anticoagulated samples are used, the choice of 1.8- or 3.6-mL citrated tubes has been shown to not make a difference; however, care should be taken to fill the tubes completely.[82]

Analytic variability also exists. Basic test preparation such as ensuring the ROTEM machine in the mobile mode is up to temperature can be easily controlled. User variability in pipetting, reagent stability, and the maintenance and calibration of equipment however are much more difficult to control and can all impact the output values. Individual tests run on different units, between different channels of the same unit, between morning and afternoon measurements show a high

degree of variability.[83] In the National External Quality Assessment Scheme surveys, as discussed earlier, high variability and poor reproducibility of the test results were seen even when the same sample was run on the same machine by the same technologist.[70]

Recommendation of the Consensus Panel

There are multiple factors that impact viscoelastic testing results.

Normal viscoelastic test results can be seen in patients with mechanical bleeding or significant coagulopathy caused by hypothermia, acidosis, warfarin and other oral anticoagulant medications, von Willebrand's disease, platelet inhibitors, and platelet dysfunction.

QUESTION 9. WHAT IS THE BEST LOCATION FOR THE VISCOELASTIC TESTING UNIT AND WHO SHOULD OPERATE THIS EQUIPMENT?

These viscoelastic tests can be run either as point-of-care tests at the bedside or as core laboratory–based tests. Having the unit located in the emergency department or operating room allows for faster time to delivery of results; however, this requires a trained technologist or clinical team member in this location available to run the test. In the United States, the Clinical Laboratory Improvements Act of 1988 allows the device to be used as a point-of-care test or as a laboratory instrument. In Europe, where hematology and blood bank are a combined specialty for laboratory technologists, having the device in the Blood Bank allows the transfusion staff to monitor the need for components and work with a transfusion medicine specialist to manage the blood therapy. Even if performed at a centralized core laboratory, these results can be immediately processed and visualized in real time by the clinical team on a variety of platforms including clinician handheld devices. To date, there are insufficient data comparing bedside and core laboratory–run samples. Ultimately, how viscoelastic testing is integrated into a specific system will depend on local factors such as the physical infrastructure and human resources.

Recommendation of the Consensus Panel

The optimal location for equipment setup is institution dependent but should allow for rapid testing and communication to the clinical team if it is to be used for the early resuscitation of bleeding trauma patients. Viscoelastic testing can be used as a point-of-care test.

Testing should also meet the local regulations that govern laboratory testing in this location.

The person(s) performing the tests and interpreting the results should be trained and educated adequately.

Further refinement of the technology for performing the test, improving throughput, and for the transfer of results to the medical record is required.

AUTHORSHIP

K. I. contributed to data interpretation, guidelines derivation, writing, and critical revision. S.R., P.V., J.C., R.D., J.H., M.M., D.B., K.B., A.C., M.P.C., J.C., B.A.C., N.C., D.F., D.F., K.G., T.H., K.K., W.M., B.N., S.S., H.S., M.S., and O.T. contributed to data interpretation, guidelines derivation, and critical revision.

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DISCLOSURE

The authors declare no conflicts of interest.

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