American Journal of Clinical Pathology
ajcp.ascpjournals.org

doi: 10.1309/AJCPPZ4J6CAFYDVM
(2010) American Journal of Clinical Pathology, 134, 97-102.

A Novel Thromboelastographic Score to Identify Overt Disseminated Intravascular Coagulation Resulting in a Hypocoagulable State

Prashant Sharma, MD, DM and Renu Saxena, MD

[+] Author Affiliations

Address correspondence to Dr Saxena: Dept of Haematology, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029, India.

Abstract

Thromboelastography (TEM) yields a multitude of data that are complicated to analyze. We evaluated its value in identification of global coagulopathy in overt disseminated intravascular coagulation (DIC). We studied 21 patients, each with International Society for Haemostasis and Thrombosis scores of 5 or more (compatible with overt DIC) and less than 5 (suggestive of nonovert DIC), who underwent whole blood nonadditive TEM. A TEM score based on the reaction and κ times, α angle, and maximum amplitude was defined as the total number of TEM parameters deranged in the direction of hypocoagulability.

The TEM score at a cutoff of 2 or more achieved sensitivity of 95.2%, specificity of 81.0%, and the highest receiver operating characteristic area under the curve of all parameters of 0.957 for identifying overt DIC. Individual TEM parameters correlated variably with conventional tests. Their combination into a cohesive TEM score possibly better captured the multiple hemostatic derangements occurring in DIC. The TEM score may bring objectivity to the analysis of TEM data.

Key Words:
Bleeding diathesis | Consumptive coagulopathy | D-dimer | Disseminated intravascular coagulation | Global test of clotting | International Society on Thrombosis and Haemostasis scoring algorithm

Disseminated intravascular coagulation (DIC) is a relatively commonly suspected complication in myriad clinical situations in hospital settings. Laboratory testing for DIC is always urgent and requires frequent repetitions to establish a diagnosis and to monitor the effect of interventions. Current strategies, owing to the multifaceted nature of DIC, need to rely on assessing multiple hemostatic and coagulation parameters to achieve adequate sensitivity and specificity. The results need to be interpreted in close correlation with the clinical data, including the primary diagnosis, presence of bleeding and/or thrombosis, and therapies administered, especially blood product support.[1]

These reasons highlight a strong need for the development of a point-of-care testing system to accurately and reliably diagnose DIC. Thromboelastography (TEM), an old technology, is promising in this regard because it provides an extended reflection of clot initiation, propagation, and lysis in whole blood.[2] The present study was planned to evaluate TEM in a hospital setting. As a "gold standard" for diagnosis, the established scoring algorithm of the International Society for Haemostasis and Thrombosis (ISTH) for overt DIC was used.[1]

Materials and Methods

This prospective study was carried out in the coagulation laboratory of a tertiary-care referral hospital. The study was cleared by the institutional ethics committee. ISTH scores were calculated for patients with an underlying disorder known to be associated with overt DIC referred for the first time for diagnostic laboratory testing Table 1.[1] Platelet counts were done on a Sysmex XT1800i hematology analyzer (Sysmex, Kobe, Japan) on EDTA-anticoagulated blood samples. The prothrombin time (PT) using STA Neoplastine and the fibrinogen level using FIBRI-PREST AUTOMATE 2 kits (Diagnostica Stago, Taverny, France) were estimated on platelet-poor plasma separated from 4.5 mL of blood in 0.5 mL of 3.2% trisodium citrate dehydrated on a STA Compact automated hemostasis analyzer (Diagnostica Stago, Gennevilliers, France). A plasma quantitative D-dimer assay was performed using the VIDAS D-Dimer Exclusion kit (quantitative enzyme-linked fluorescence assay; bioMérieux, Marcy l'Etoile, France) on the mini-VIDAS analyzer (bioMérieux).

Based on the calculated ISTH score, the following study groups were defined and tested further: (1) group 1 (overt DIC), 21 patients with an underlying disorder known to be associated with overt DIC and with an ISTH score of 5 or more; and (2) group 2 (control subjects without overt DIC), 21 patients with an underlying disorder known to be associated with overt DIC but with an ISTH score of less than 5.

Whole blood nonadditive TEM was performed on the TEM-A automated thromboelastometer (Framar Biomedica, Rome, Italy). Four classical TEM parameters were recorded Figure 1: reaction (R) time, normal range, 450 to 690 seconds; κ time, normal range, 240 to 390 seconds; α angle, normal range, 36° to 48°; and maximum amplitude (MA), normal range, 34 to 46 mm.

View this table:
In this window In a new window

Table 1

The ISTH Scoring System for Overt DIC[1*]

TEM Score for DIC The 4 basic TEM parameters most likely to be deranged in DIC were determined to be R time, κ time, α angle, and MA. A novel TEM score (range, 0-4) was defined as the total number of parameters of these 4 that were deranged in any given case toward hypocoagulability, ie, prolonged R and κ times and shortened α angle and MA. Lysis parameters were excluded from the TEM score because these indices are calculated by the thromboelastograph only after a minimum run of about an hour, thus defeating the purpose of point-of-care testing, and these values were not found to be deranged in previous research on DIC.[3,4]

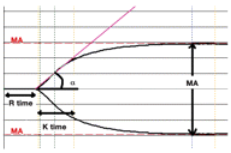
Statistical Analysis Descriptive statistics were analyzed for individual tests. The significance of differences between subgroups was tested by using the Fisher exact test, paired *t* test, or the Mann-Whitney test. *P* values less than .05 were considered significant. Accuracy indices (sensitivity, specificity, and negative and positive predictive values) were calculated for each assay using the ISTH score as the reference gold standard. Receiver operating characteristic (ROC) curves were constructed to generate optimal cutoffs for the different tests. The area under the curve (AUC) was calculated to compare relative diagnostic efficiencies for each assay. All analyses were done using SPSS for Windows, version 11.5 (SPSS, Chicago, IL).

Results

When compared by measures of central tendency, virtually all parameters were significantly different between the patients with and without overt DIC Table 2 and Table 3.

Figure 1

A normal thromboelastography tracing depicting reaction (R) time, κ (K) time, α angle, and maximum amplitude (MA).



View larger version:
In this page In a new window

The performance results of the individual conventional laboratory tests and TEM parameters are given in Table 4. No individual conventional laboratory test or any individual TEM parameter taken alone showed sensitivity and specificity of more than 90%. No diagnostic test for overt DIC other than MA on TEM showed an AUC of more than 0.9 in ROC curve analysis at any cutoff generated (Table 4). These findings imply that the individual tests, although useful, are less efficient than the ISTH score (reported sensitivity, 93%; specificity, 98%; positive predictive value, 96%; and negative predictive value, 97%) at a cutoff of 5 or more for overt DIC.[5]

Nearly all patients in group 1 had TEM tracings suggestive of variable degrees of hypocoagulability. Suggestive TEM patterns were seen in nearly 8 patients of 21, but interpretation of the visual pattern alone was subjective Figure 2. For calculating diagnostic accuracy, therefore, the numeric TEM parameters were analyzed.

Correlation Between TEM and Individual Conventional Coagulation Parameters The correlation coefficients, *r*, of all 4 TEM parameters vs the platelet count, PT, and fibrinogen and quantitative D-dimer levels are given in Table 5.

The interrelationships of TEM with conventional parameters were of variable strength but were all in the expected directions. The α angle and MA correlated best with the conventional parameters.

View this table:
In this window In a new window

Table 2

Results of Individual Conventional (ISTH Score) Parameters*

View this table:
In this window In a new window

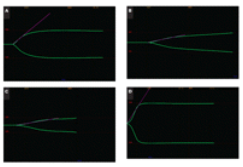
Table 3

Results of Individual Thromboelastography Parameters*

View this table:
In this window In a new window

Table 4

Individual Test Performance: Receiver Operating Characteristic Curve Analysis for Generation of Cutoffs and Calculation of the AUC



View larger version:
In this page In a new window

Figure 2

A, A normal thromboelastography tracing with normal reaction (R) and κ times, maximum amplitude (MA), and the α angle. **B**, Tracing from a patient with overt disseminated intravascular coagulation (DIC) shows prolonged R and κ times, very low angle, and low MA. **C**, A patient with overt DIC by the International Society on Thrombosis and Haemostasis (ISTH) score shows nearly normal R and κ times but with even lower MA. **D**, A tracing suggestive of a hypercoagulable state (short R time, high MA, and large α angle) from a patient with myeloma with a falling hemoglobin level and an ISTH score <5.

Individual TEM Parameters in Testing for DIC Independent accuracy statistics are given in Table 4. The MA was the most sensitive and specific of the TEM parameters. At the generated cutoff of 32 mm, it had 85.7% sensitivity with 90.5% specificity. In terms of the ROC analysis, MA was the only individual parameter with an AUC more than 0.9. However, 5 (24%) of 21 patients with ISTH scores less than 5 also had an MA of more than 34 mm, the lower normal limit.

View this table:
In this window In a new window

Table 5

Correlation Coefficients of TEM vs Conventional Coagulation Parameters*

Diagnostic Performance of the "TEM Score 2 or More" Criterion The distribution of TEM scores (0–4) for 42 patients is given in Figure 3. The TEM score of 2 or more (ie, at least 2 of the 4 variables, R time, κ time, α angle, and MA, deranged in the direction of hypocoagulability at the ROC-generated cutoff) achieved a sensitivity of 95.2% and a specificity of 81.0%. The AUC was the highest in this study at 0.957.

Discussion

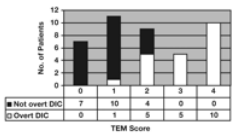
Point-of-care diagnosis of DIC is a highly desirable goal. Testing may be required at any time and is usually an emergency STAT request. Laboratory results in an appropriate clinical backdrop are essential to establish the diagnosis, guide therapy, and predict prognosis. Repeated testing is often required for the diagnosis and to assess the effect of therapeutic interventions.[1]

The current standard-of-care diagnostic strategy, the ISTH scoring system, relies on 4 widely available assays to generate a score.[1] However, these parameters are difficult to standardize and control for quality outside the laboratory. This study was therefore planned with a view to assess TEM as a promising rapid test for DIC. An important consideration for selecting TEM was that it is already available in point-of-care applications in our institution for indications other than the diagnosis of DIC.

There has been a resurgence of interest in TEM for the assessment of global coagulation changes in bleeding disorders. It is in use at many centers to aid transfusion decisions.[2–12] In the individual parameters, the high AUC and the best tradeoff between sensitivity and specificity of MA among all our tests,

followed by α angle and κ time, is remarkably similar to findings by Sivula et al,[3] who found the maximum clot firmness, clot formation time, and α angle to discriminate DIC from other conditions. Their study and other studies using TEM in DIC are summarized in Table 6.[3,4,6,9–12]

Virtually all deranged TEM parameters in the 21 overt DIC cases were in the direction of hypocoagulability. From the visual analysis, it was clear that different cases had differing combinations of derangements. Because each TEM parameter itself correlates with multiple conventional parameters (eg, R time with coagulation factors and platelets and MA with fibrinogen and platelets), the picture that emerged from TEM needed clarification.



View larger version:
In this page In a new window

Figure 3

Distribution of thromboelastography (TEM) scores across patient groups. A discriminant value of at least 2 parameters being deranged enabled the greatest demarcation between the groups with and without overt disseminated intravascular coagulation (DIC).

The conventional parameters of the ISTH algorithm (platelet count, PT, fibrinogen, and D-dimer) are less useful individually than when combined into a cohesive score that better captures the multifactorial derangements in hemostasis occurring in DIC. An analogous situation exists for TEM. The TEM score is designed to maximize the detection of a hypocoagulable state (exemplified by advanced-stage DIC) with depletion of the enzymatic phase (coagulation factors), cellular phase (thrombocytopenia), and substrate (fibrinogen).

View this table:
In this window In a new window

Table 6

Summary of Major TEM-Based Studies on DIC and Related Disorders

The diagnosis of overt DIC is a clinical and laboratory exercise, and the exclusion of other close and often related differential diagnoses is vital. The TEM score is a useful adjunct in this process but may be of limited usefulness in cases with marked thrombocytopenia such as immune thrombocytopenia, thrombotic thrombocytopenic purpura, and heparin-induced thrombocytopenia and thrombosis. Cases of these 3 entities were not a part of the 21 group 2 patients. This could be a sampling bias owing to the small cohort studied or may reflect the fact that the clinical backgrounds and manifestations and the baseline investigation results in such situations may have led to a lower index of suspicion for overt DIC. However, in cases with an overlapping clinical phenotype, the distinction of heparin-induced thrombocytopenia and thrombosis and thrombotic thrombocytopenic purpura from overt DIC would be crucial to determine therapy (choice of an alternative anticoagulant and decision to start plasmapheresis respectively). Other groups, eg, postoperative patients who received massive transfusion and patients with fulminant hepatic coagulopathy, will also likely have false-positive TEM score results, but the changes in clinical management may be less critical.

From another perspective, point-of-care TEM-based algorithms that guide transfusion, factor replacement, and anticoagulant-reversal therapies in patients undergoing major cardiothoracic and vascular surgeries currently rely on the activated R time, MA, and lysis indices supported, in some cases, by platelet counts and fibrinogen levels.[13] Because these intraoperative and postoperative states are marked by multifactorial hypocoagulability and a risk of thrombosis analogous to DIC, it is interesting to speculate whether analyzing combinations of thromboelastographic parameters like the TEM score may be of clinical value in these settings.

A thorough literature search did not reveal prior scoring of the TEM output data in overt DIC to generate a consolidated picture. Further studies validating this parameter in overt DIC in specific patient subsets and analyzing its usefulness in providing a synoptic view of extra data provided by TEM in other situations are indicated.

The newly designed TEM score is a promising, highly sensitive adjunct to conventional tests in accurately identifying overt DIC. It consolidates and enhances interpretation of the otherwise multitude of data obtained from the thromboelastogram.

Acknowledgments

We thank Rakesh Kumar Ahuja, PhD, Department of Biostatistics, AIIMS for statistical analysis; Arijit Biswas, PhD, for various kit-related assistance; and Suresh Ditta, Suresh Kumar, and Rajesh Jaiswal for coordinating the laboratory testing.

References

1. Taylor FB Jr, Toh CH, Hoots WK, et al; for the Scientific Subcommittee on Disseminated Intravascular Coagulation (DIC) of the International Society on Thrombosis and Haemostasis (ISTH). Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thromb Haemost. 2001;86:1327–1330. Medline Google Scholar

2. Chen A, Teruya J. Global hemostasis testing thromboelastography: old technology, new applications. Clin Lab Med. 2009;29:391–407. Medline Google Scholar

3. Sivula M, Pettilä V, Niemi TT, et al. Thromboelastometry in patients with severe sepsis and disseminated intravascular coagulation. Blood Coagul Fibrinolysis. 2009;20:419–426. Medline Google Scholar

4. Daudel F, Kessler U, Folly H, et al. Thromboelastometry for the assessment of coagulation abnormalities in early and established adult sepsis: a prospective cohort study. Crit Care. 2009;13:R42. doi:10.1186/cc7765. Medline Google Scholar

5. Bakhtiari K, Meijers JC, de Jonge E, et al. Prospective validation of the International Society of Thrombosis and Haemostasis scoring system for disseminated intravascular coagulation. Crit Care Med. 2004;32:2416–2421. CrossRef Medline Google Scholar

6. Levrat A, Gros A, Rugeri L, et al. Evaluation of rotation thrombelastography for the diagnosis of hyperfibrinolysis in trauma patients. Br J Anaesth. 2008;100:792–797. Abstract/FREE Full Text

7. Spiel AO, Mayr FB, Firbas C, et al. Validation of rotation thrombelastography in a model of systemic activation of fibrinolysis and coagulation in humans. J Thromb Haemost. 2006;4:411–416. CrossRef Medline Google Scholar

8. Zacharowski K, Sucker C, Zacharowski P, et al. Thrombelastography for the monitoring of lipopolysaccharide induced activation of coagulation. Thromb Haemost. 2006;95:557–561. Medline Google Scholar

9. Moopanar D, Naidu S, Moodley J, et al. Thromboelastography in abruptio placentae. J Obstet Gynaecol. 1997;17:229–233. Medline Google Scholar

10. Kheirabadi BS, Crissey JM, Deguzman R, et al. In vivo bleeding time and in vitro thrombelastography measurements are better indicators of dilutional hypothermic coagulopathy than prothrombin time. J Trauma. 2007;62:1352–1361. Medline Google Scholar

11. Collins PW, Macchiavello LI, Lewis SJ, et al. Global tests of haemostasis in critically ill patients with severe sepsis syndrome compared to controls. Br J Haematol. 2006;135:220–227. CrossRef Medline Google Scholar

12. Grant HW, Hadley GP. Prediction of neonatal sepsis by thromboelastography. Pediatr Surg Int. 1997;12:289–292. CrossRef Medline Google Scholar

13. Ak K, Isbir CS, Tetik S, et al. Thromboelastography-based transfusion algorithm reduces blood product use after elective CABG: a prospective randomized study. J Card Surg. 2009;24:404–410. CrossRef Medline Google Scholar