Thromboelastography in the Management of Coagulopathy Associated With Ebola Virus Disease

Andrew J. Wilson,1 Daniel S. Martin,2 Victoria Maddox,2 Simon Rattenbury,3 Davis Bland,4 Sanjay Bhagani,1 Ian Cropley,1 Susan Hopkins,5 Stephen Mepham,2 Alison Rodger,2 Simon Warren,3 Pratima Chowdary,1 and Michael Jacobs3

1Katharine Dormandy Haemophilia Centre and Thrombosis Unit, Royal Free London NHS Foundation Trust, 2Division of Surgery, University College London, and 3Department of Infection, Royal Free London NHS Foundation Trust, United Kingdom; 4Haemonetics Corporation, Braintree, Massachusetts; and 5Research Department of Infection and Population Health, University College London, United Kingdom

Here, we describe the first use of thromboelastography (TEG) in the management of 2 cases of Ebola virus disease. Early in their illness, both patients had evidence of a consumptive coagulopathy. As this resolved, TEG demonstrated that both developed a marked hypercoagulable state, which was treated with low-molecular-weight heparin.

Keywords. Ebola; thromboelastography; coagulopathy; clotting.

The current Ebola virus disease (EVD) outbreak in West Africa is unprecedented in scale, with more than 28,000 cases reported by November 2015 [1]. While clinically significant hemorrhage occurs in only a minority of patients, minor hemorrhagic manifestations are more common [2–4], and coagulopathy appears to be a typical feature of EVD [5–7]. Detailed studies of the coagulation pathway in human EVD cases have been limited by the technical difficulties of working in the field and in high-containment facilities. Disseminated intravascular coagulation (DIC) is believed to be a significant component of the coagulopathy; elevated d-dimers and thrombocytopenia are consistently observed in early stages of illness [5–7]. Elevated thrombomodulin levels [7] suggest that endothelial cell injury may be a trigger for DIC. Data from nonhuman primate models of EVD support the existence of DIC [8] and suggest that increased tissue factor expression and endothelial cell injury in response to inflammation may be key triggers [9–11].

Given our limited understanding of the complex balance between bleeding and thrombotic abnormalities at various stages of EVD, rational clinical management of the hemostatic abnormalities is challenging. In the current EVD outbreak, a few individuals have been medically evacuated to healthcare facilities in resource-rich countries, which has permitted the use of investigative and therapeutic techniques unavailable in most facilities in West Africa. Here, we report the use of thromboelastography (TEG) to inform the clinical management of coagulation abnormalities as they evolved over the course of EVD in 2 cases treated in the Royal Free Hospital, London.

PATIENT 1

A 39-year-old nurse who had provided direct patient care in an Ebola treatment unit in Sierra Leone was diagnosed with EVD following her return to the United Kingdom. She was admitted to the high-level isolation unit at the Royal Free Hospital on day 3 of illness, at which time she was febrile but otherwise well. Her admission blood tests demonstrated normal platelet count (242 × 109/L), prothrombin time (PT; 13 seconds, control <13.2 seconds), and activated partial thromboplastin time (APTT; 37 seconds, control <48.8 seconds; Figure 1A) and negative d-dimers. She had a moderate Ebola viral load by reverse-transcription polymerase chain reaction (cycle threshold [Ct] = 24) [12]. A central venous catheter was inserted, and her care was focused on assiduous fluid and electrolyte monitoring. She was started on standard low-molecular-weight heparin (LMWH) prophylaxis against thromboembolic disease (tinzaparin, 4500 U once daily), and received 2 pools of convalescent plasma from an EVD survivor on consecutive days. By day 5 of illness, her clinical condition had deteriorated, with diarrhea, respiratory failure that required noninvasive ventilatory support, and oozing from around the venous catheter insertion site. Her viral load had increased (Ct = 15) and she had blood tests suggestive of a consumptive coagulopathy: low platelets (114 × 109/L), prolonged PT (16 seconds) and APTT (68 seconds; Figure 1A), and elevated d-dimers (1200 ng/mL). In view of the bleeding risk, LMWH was withheld.

Monoclonal antibody therapy specific for the Ebola virus glycoprotein (ZMab; Public Health Agency of Canada) was administered on days 5 and 8 of illness, and her clinical condition and coagulation function slowly improved. In order to understand better the coagulopathy in this and potential future patients and to guide product replacement, if needed, a TEG 5000 analyzer (Haemonetics Corporation, Braintree, Massachusetts) was obtained for TEG. As the patient continued to recover, she developed progressive thrombocytosis (maximum platelet count, 1726 × 109 on day 21 of illness; Figure 1A). TEG traces showed progressive shortening of the reaction (R) time and an increase in maximum amplitude (MA) of clot formation, as well as an increase in the maximum rate of thrombus generation (MRTG).
and a decrease in the time to maximum rate of thrombus generation (TMRTG; Figure 1B). Taken together, these findings were consistent with evolving hypercoagulability. She was treated with low-dose aspirin (75 mg once daily), and the dose of tinzaparin was increased. This was subsequently converted to treatment-dose enoxaparin (60 mg twice daily) in view of TEG findings suggestive of heparin resistance (R times in paired samples with and without heparinase showed no significant difference). When ambulant and fit for discharge, the patient was given an intermediate dose of enoxaparin (60 mg once daily) as empiric prophylaxis against thromboembolic disease. This was given for 4 weeks post-discharge without complications. Aspirin was stopped at 2 weeks post-discharge when the platelet count fell below \(600 \times 10^9/L\).

**PATIENT 2**

A 25-year-old female nurse was diagnosed with EVD at the Ebola treatment unit where she was working in Sierra Leone. Treatment was started in-country with an experimental antiviral agent, favipiravir. She was medically evacuated to the Royal Free Hospital, where she was admitted on day 5 of illness. On admission, she was febrile but generally well, with a low platelet count \((95 \times 10^9/L)\), slightly prolonged PT (15 seconds) and normal APTT (28 seconds; Figure 1C), and a moderate to high viral load \((Ct = 20)\) [12]. A central venous catheter was inserted, and she was treated with intravenous fluids, tinzaparin 4500 U once daily for prophylaxis against thromboembolic disease, and Ebola virus glycoprotein-specific monoclonal antibody therapy (MIL77, Beijing Mabworks, China). Over the next 3 days, she developed profound weakness, anorexia, and diarrhea. She had no clinical evidence of bleeding. Her blood tests were compatible with a progressive consumptive coagulopathy, with decreasing platelet count \((49 \times 10^9/L)\), prolongation of PT (16 seconds) and APTT (63 seconds; Figure 1C), and elevated d-dimers \((1600 \text{ ng/mL})\). In keeping with this, TEG demonstrated increasing R time and TMRTG with reduced MRTG and MA (Figure 1D). LMWH was therefore withheld. She was treated with a second dose of MIL77 on day 8 of illness; subsequently, the patient gradually improved clinically and all symptoms resolved. The platelet count, PT, and APTT normalized (Figure 1C) and d-dimers became negative. Later in the recovery phase, she developed evidence of a hypercoagulable state, with

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**Figure 1.** Changes in blood, coagulation, and thromboelastography (TEG) parameters against day of illness are shown for patient 1 (panels A and B) and patient 2 (panels C and D). Values for hemoglobin, prothrombin time, activated partial thromboplastin time, and platelets are shown in the upper panels. Lower panels show the following key TEG parameters: maximum rate of thrombin generation, time to maximum rate of thrombin generation, maximum amplitude of clot formation, and reaction time. On all graphs, the left-hand y axis pertains to the units (shown in figure legend) for solid lines and the right-hand y axis pertains to the units for the dotted lines. Abbreviations: APTT, activated partial thromboplastin time; Hb, hemoglobin, MA, maximum amplitude of clot formation; MRTG, maximum rate of thrombin generation; Plts, platelets; PT, prothrombin time; R, reaction time; TMRTG, time to maximum rate of thrombin generation.
shortened the R time and TMRTG and an increase in MA and MRTG (Figure 1C and 1D). The tinzaparin dose was increased and ultimately converted to treatment-dose enoxaparin in view of evidence of heparin resistance on TEG. The patient completed 2 weeks of intermediate-dose enoxaparin (60 mg once daily) on discharge without complications.

**DISCUSSION**

TEG is a point-of-care test that measures coagulation factor function, platelet function, clot strength, and fibrinolysis (see Supplementary Material). Prior to introduction of TEG into our high-level isolation unit, coagulation parameters were limited to measurement of platelet count, PT, APTT and a semiquantitative d-dimer assay. There was concern that should EVD patients develop significant bleeding, there would be insufficient laboratory information for rational choice and monitoring of blood product replacement; in particular, the adequacy of fibrinogen replacement with fresh frozen plasma, cryoprecipitate, or fibrinogen concentrate. Both of our cases developed evidence of a consumptive coagulopathy early in infection, but neither had significant hemorrhage nor required blood product replacement, which has been a common observation during the current Ebola outbreak [2–4].

Functional clotting tests returned to normal in the recovery phase. However, in both patients TEG revealed hypercoagulability, which would not have been evident from conventional clotting tests and has not been described previously in the recovery phase of EVD. The pathophysiology is unknown but most likely relates to endothelial injury during the acute phase of infection complicated by consumptive coagulopathy, followed by an acute phase response that includes elevation of platelet count, fibrinogen, and potentially von Willebrand factor and factor VIII, manifesting as hypercoagulable TEG tracings. Given the lack of available tests in the field, it is not known whether development of a hypercoagulable state during recovery is a common feature of EVD. We previously cared for 1 other EVD patient in our unit with relatively mild clinical disease. He did not develop thrombocytosis during the recovery phase; TEG was not available at the time.

Given the lack of data, it is unclear whether specific treatment of the observed hypercoagulability in the recovery phase of EVD affects outcome. We determined that anticoagulation with treatment-dose LMWH was warranted on the basis of the laboratory parameters that, together with reduced patient mobility, implied a high risk of venous thromboembolic disease (see Supplementary Material). During tinzaparin treatment, TEG suggested possible heparin resistance, and so both patients were ultimately treated with enoxaparin, the action of which is not as influenced by the acute-phase response. Neither case developed any clinical evidence of venous thromboembolic disease or complications from anticoagulation.

We observed a complex disturbance in hemostasis that evolved similarly over the course of treatment for the 2 EVD cases. In the acute phase of illness, both patients developed evidence of consumptive coagulopathy; in recovery, both showed evidence of hypercoagulability. TEG provided a simple, point-of-care methodology to define and monitor the progression of the coagulopathy and direct rational treatment decisions. More investigations directed toward understanding the coagulation disturbances along with TEG data would further our understanding of the spectrum and evolution of clotting abnormalities in EVD and other viral hemorrhagic fevers.

**Supplementary Data**

Supplementary materials are available at http://cid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

**Notes**

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**References**