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Blood component therapy guided by celite-activated thromboelastography for perioperative coagulopathy

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Introduction

Thromboelastography (TEG) is a viscoelastic measurement of clot formation, originally described by Hartert in 1948 [1]. Multiple parameters can be obtained from the TEG trace (Fig. 1c, Table 1). Clinically, TEG was shown to be effective in guiding transfusion therapy in the early days of liver transplantation [2]. Further modifications of TEG, including celite activation and heparinase, have been introduced, making TEG a "point-of-care" coagulation monitor in a wide variety of surgical procedures [3–7]. At our institution, TEG with celite activation is performed in the operating room by anesthesiologists. Briefly, the blood sample is collected from the existing arterial line using a two-syringe technique. One milliliter of the whole blood sample is placed in a vial containing 90 μl of celite particles in normal saline (1% celite concentration), and, after being mixed by inversion five times, 0.36 ml of the whole blood is pipetted into a prewarmed plastic cup (37°C). With the use of celite as a coagulation activator, the blood is activated more rapidly and homogeneously, leading to a more rapid assessment of coagulation status. Reduced time for obtaining the maximum amplitude and lysis index is a clear advantage over the conventional TEG [7,8]. We report three patients in whom on-site TEG (C-TEG3000T; Haemoscope, Niles, IL, USA) was useful in monitoring coagulation status and guiding the blood component therapy.

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Case 1

Case 1 was a 54-year-old man (weight, 65 kg; height, 160 cm), who while a bicycling was involved in a head-on collision with a truck. He was brought to the emergency room with findings of a slightly depressed level of consciousness (Glasgow Coma Scale [GCS]-II score of 4). His abdomen was distended, and computed tomography (CT) scanning revealed a high-resolution lesion that was widespread throughout the mesentery, consistent with intraabdominal bleeding. He was orally intubated, and 1800 ml of packed red blood cells (RBC) was administered in the emergency room.

Subsequently, he was brought to the operating room for exploratory laparotomy. General anesthesia was maintained with O_2 and sevoflurane. We were not able to detect any clot formation on celite-activated TEG immediately after induction of anesthesia (Fig. 1A). The patient showed continuous bleeding, which required crystalloid 5700 ml; RBC 3600 ml; and fresh frozen plasma (FFP), 1200 ml. Tranexamic acid 1500 mg was given because increased fibrinolysis was also suspected from the minimal clot formation. Blood loss was estimated as 12000 ml by the time surgical hemostasis was established. Subsequent TEG showed near-normal reaction (R) time (8.3 min), but severely decreased α angle and maximum amplitude (MA; 23° and 19 mm), suggesting decreased platelet count (Fig. 1B). It also showed hyperfibrinolysis (Lysis index at 60 min [LY_{60}], 17.5%). Platelet count was measured together with the second TEG, and it was 23000/mm^3, consistent with a reduced α angle and MA. Thirty-five units of platelets, FFP 560 ml, and tranexamic acid 1000 mg were given. At the end of the surgery, TEG showed near-normal values (Fig. 1C; R, 2.5 min; α, 54°; MA, 47 mm; and LY_{60}, 5.5%).

There was no increased bleeding from the drainage tube after the operation.

Table 1. TEG-guided coagulation management

TEG	Value	Clinical implications	Treatment
R	10.5–14 min	↓ Coagulation factors	FFP 8 ml/kg
R	>14 min	↓↓ Coagulation factors	FFP 16 ml/kg
MA	40–48 mm	↓ Platelet function or count	Platelet 1 unit/10 kg
MA	<40 mm	↓↓ Platelet function or count	Platelet 2 unit/10 kg
MA	>75 mm	↑ Fibrinogen or ↑ platelet count	Anticoagulation[a]
LY30	>7.5%	Hyperfibrinolysis	Tranexamic acid
LY60	>15%	Hyperfibrinolysis	Tranexamic acid

Modified from von Kier and Royston [11]
TEG, Thromboelastography; R, reaction (time); MA, maximum amplitude; LY30, Lysis index at 30 min; LY60, Lysis index at 60 min; FFP, fresh frozen plasma
[a] When clinically indicated

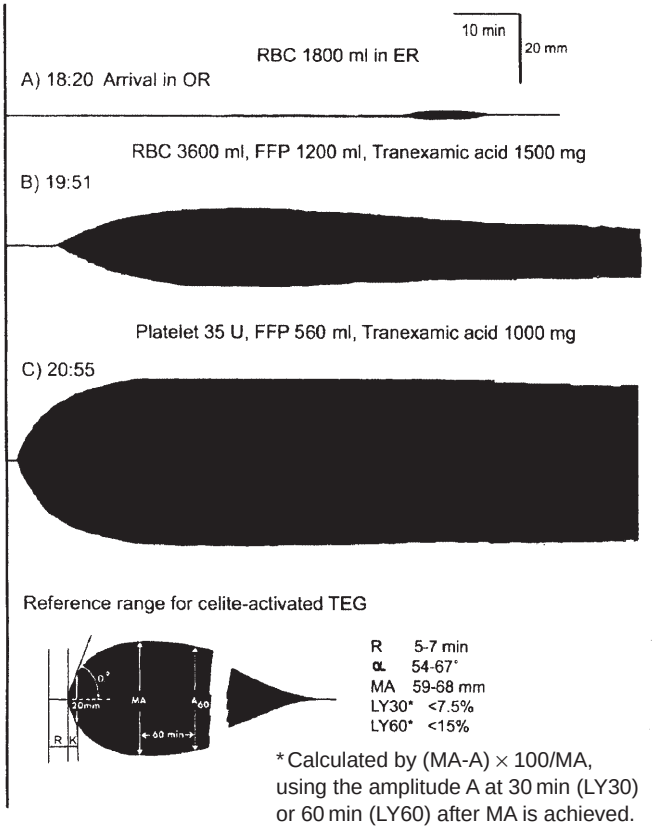

Fig. 1A–C. Case 1. **A**, **B**, and **C** show thromboelastography (TEG) performed at the times shown. Based on the TEG result, suitable blood products and/or tranexamic acid were administered, as indicated under the respective trace. Reference range data were obtained from the C-TEG3000T (Haemoscope, Niles, IL, USA). *ER*, Emergency room; *OR*, operating room; *RBC*, red blood cells; *FFP*, fresh frozen plasma; *R*, reaction (time); α, alpha angle; *MA*, maximum amplitude, *LY30*, Lysis index at 30 min; *LY60*, Lysis index at 60 min

Case 2

Case 2 was a 28-year-old woman, a primigravida (weight, 62.5 kg; height, 158 cm), at 41 weeks of gestation, who was admitted because of abdominal pain and dizziness. She had no significant past medical history. Decreased fetal heart rate and placental hemorrhage were observed on an ultrasonogram, and abruptio placentae with fetal distress was diagnosed. She was brought to the operating room for emergency cesarean section. The preoperative laboratory data were as follows: WBC, 24 000/mm^3; hemoglobin, 11.7 g·dl^{-1}; hematocrit, 35.1%; and platelet count, 96 000/mm^3. Coagulation tests such as prothrombin time PT international normalized ratio [INR], 3.36; activated partial thromboplastin time (APTT), 77.6 s; and fibrinogen, less than 50 mg·dl^{-1}, suggested a consumptive coagulopathy. No marked changes in serum electrolyte values were noted.

The patient was orally intubated and general anesthesia was maintained with O_2/N_2O initially, and with O_2/N_2O with sevoflurane after the fetus was delivered dead. Massive hemorrhage occurred when the placenta was delivered. The initial celite-TEG suggested severe fibrinolysis (R, 17.5 min; MA, 1 mm; LY60, 100%) (Fig. 2A). Tranexamic acid 1500 mg was administered along with RBC 1680 ml, and FFP 1600 ml. Two hours after the initial treatment, vital signs were stabilized, and we measured the second TEG (Fig. 2B), which showed resolution of the hyperfibrinolysis. However, the R time (15.3 min) was twice the normal level, and the α angle (25.5°) and MA (30.5 mm) were nearly half the normal values, suggesting deficiencies of both coagulation factors and platelets. The platelet count, measured simultaneously with the second TEG, was 52 000/mm^3. Based on these results, FFP 800 ml and 20 units of platelets were administered. A third TEG was obtained at the end of surgery (Fig. 2C). There were significant improvements in the α angle (57.5°) and MA (53 mm) with a slight prolongation of R time (9.5 min). The patient was transferred to the intensive care unit (ICU) in stable condition. She did not require other blood products, except for RBC 720 ml for anemia while in the ICU.

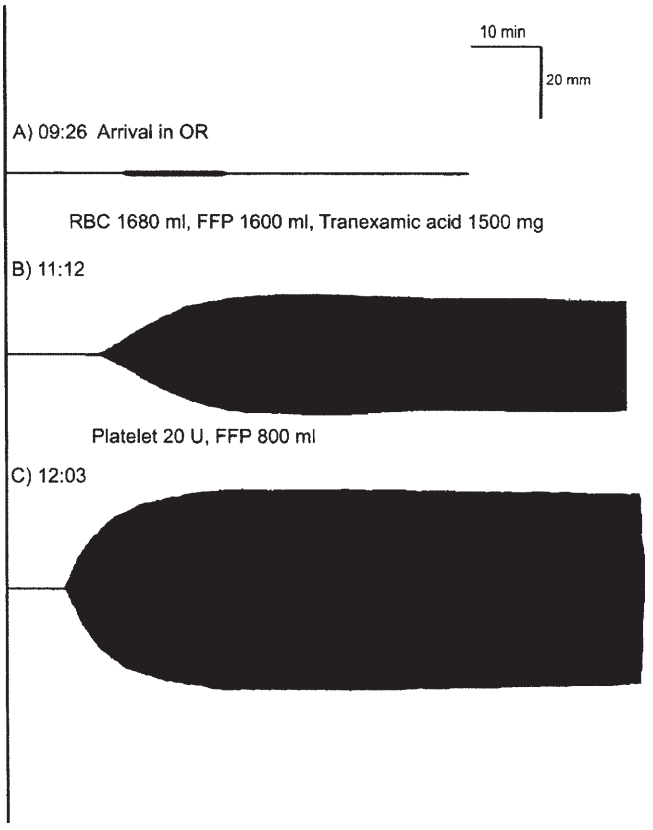

Fig. 2A–C. Case 2. **A**, **B**, and **C** show TEG performed at the times shown. Treatment based on the TEG is indicated under the respective trace

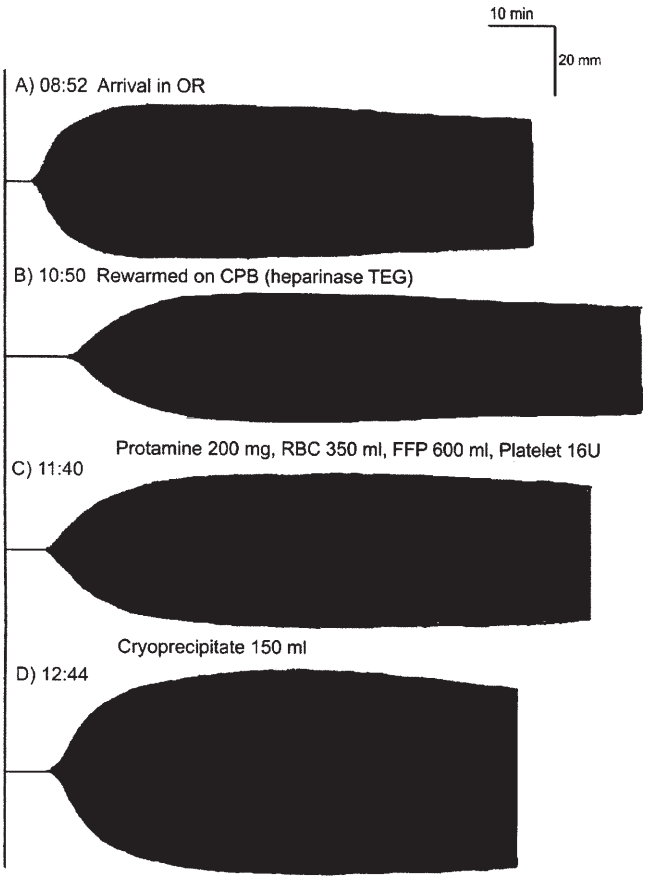

Fig. 3A–D. Case 3. **A**, **B**, **C**, and **D** show TEG performed at the times shown. Treatment based on the TEG is indicated under the respective trace. *CPB*, Cardiopulmonary bypass

Case 3

Case 3 was a 48-year-old woman (weight, 125 kg; height, 165 cm), who was scheduled for coronary artery bypass graft surgery. She had a non-Q wave myocardial infarction 3 days prior to the surgery. Cardiac catheterization showed 70% stenosis of the proximal left anterior descending (LAD) artery, 60% stenosis of the mid right coronary artery (RCA), and an estimated ejection fraction of 25%. She had a history of noninsulin-dependent diabetes mellitus, obesity, and deep venous thromboses. Her preoperative medication included amlodipine, metformin, nitroglycerin, and coumadin. Coumadin was replaced with heparin 3 days prior to the surgery.

Laboratory data showed normal electrolyte values; hematocrit was 39.5%; platelet count, 245 000/mm^3; and PT (INR), 1.30.

Anesthesia was induced with sodium thiopental, fentanyl, and pancuronium, and was maintained with isoflurane/O_2. The baseline celite-TEG was obtained with the addition of heparinase to the blood sample (4 U·ml^{-1}) to neutralize preoperatively administered heparin (Fig. 3A). The normal R time (2.5 min) suggested no significant residual effect of coumadin. The moderate reduction of MA (47 mm) suggested a dysfunction of fibrinogen-platelet interaction. Intraoperative heparin anticoagulation was monitored by the kaolin-activated coagulation time (ACT), using a Hemochron device (International Technodyne, Edison, NJ, USA). Baseline ACT was 297 s. After the administration of bovine-lung heparin 50 000 units, kaolin-ACT was more than 1000 s. Subsequently, high-dose aprotinin was administered throughout the surgery (2×10^6 KIU loading dose; 0.5 KIU·h^{-1} infusion). Two-vessel coronary bypass was performed using saphenous venous grafts during moderate hypothermia (32°C) on cardiopulmonary bypass (CPB). When the patient was rewarmed to 35.5°C, blood samples for platelet count and fibrinogen level were sent to the laboratory, and the celite-TEG with heparinase was repeated (Fig. 3B). The TEG result showed a further reduction in MA (38.0 mm), and a prolonged R time (11 min). At this point, 16 units of platelet concentrates and 2 units of FFP were ordered and thawed. The patient was weaned from the CPB with norepinephrine and milrinone infu-

sion. Protamine 200 mg was administered to neutralize heparin, and the ACT returned to 134 s. RBC 350 ml were given for low hematocrit (23%). When the preordered blood products became available, the laboratory data were also returned, which confirmed the TEG results: platelet count, 79 000/mm^3 and fibrinogen, 75 mg·dl^{-1}. After the transfusion of platelets and FFP, TEG was repeated (Fig. 3C; R, 7.3 min; α, 43°; MA, 46 mm). In addition, cryoprecipitate 150 ml was given to supplement fibrinogen. After the cryoprecipitate, the repeat TEG revealed full recovery of hemostatic function (R, 7 min; α, 57.5°; MA, 52.5 mm) (Fig. 3D). The patient was transferred to the ICU in a stable condition. She required 1000 ml of RBC to replace the total chest tube drainage of 1315 ml over 24 h, but no other hemostatic products were necessary while she was in the ICU.

Discussion

The three cases described here show the usefulness of TEG in the settings of massive hemorrhage, consumption coagulopathy, and CPB-induced coagulopathy. The conventional method for managing perioperative bleeding is the transfusion of fluid and the empirical use of blood products, with or without inotropic support to stabilize the hemodynamic parameters. Additional blood products are ordered when abnormal coagulation test results are reported. The standard laboratory coagulation tests are PT and APTT, which require citrate anticoagulation and blood centrifugation to obtain plasma. Because of their relatively long turn-around times (30–40 min), these tests are not suitable for point-of-care coagulation monitoring. Several whole blood PT/APTT monitors are available for use at the bedside, but correlations with the standard PT/APTT are questionable in complex clinical situations [9]. Equivalent information on clotting factor activity can be obtained by celite-activated TEG within 15–20 min (R time; Fig. 1), along with the quantitative measure of fibrin-platelet interaction (α and MA; Fig. 1). Modified TEG with celite, a diatomaceous earth, provides several advantages over native (nonactivated) TEG. Celite-induced factor XII activation accelerates thrombin formation, leading to more rapid assessment of coagulation status. Sharma et al. [7] reported an up to fourfold reduction in R time, and an up to 73% increase in α angle when celite-activated TEG was compared with native TEG in pregnant women. Yamakage et al. [8] also reported that celite-activated TEG resulted in an approximately 50% reduction in R time and a 19% increase in MA when compared with native TEG. In addition, detection of fibrinolysis was possible 30 min after MA with celite-activated TEG, in contrast to 60 min with native TEG.

We observed enhanced fibrinolysis in our cases 1 and 2. Systemic hyperfibrinolysis may cause perioperative bleeding, such as that seen in liver transplantation, cardiac surgery, or disseminated intravascular coagulopathy. It is not practical to order laboratory tests for fibrinolysis in acute settings, because the turn-around time for these tests (D-dimers and fibrin degradation products) is very long (several hours). On the other hand, hyperfibrinolysis can be detected on TEG within 1 h, as seen in our cases [8]. The inappropriate use of antifibrinolytic drugs, such as tranexamic acid, may result in a thrombotic condition. Therefore, it is important to monitor coagulation before and after specific treatment. In cases 1 and 2, we were able to observe the resolution of clinical fibrinolysis after the administration of tranexamic acid and FFP. Low platelet counts were observed in all three of our patients—cases 1, 2, and 3 (platelet counts, 23, 52, and 79 × 1000/mm^3, respectively). The simultaneous TEG results were all abnormal: MA, 19; 30.5, and 38 mm, respectively. Recently, Khurana et al. [10] reported that the clot strength on TEG (MA) was a function of platelet concentration. They utilized various concentrations of glycoprotein (GP) IIb/IIIa inhibitor (c7E3 Fab) to block platelet function, delineating the contribution of platelets to the clot formation. Platelet GP IIb/IIIa is a site for fibrinogen binding, which plays a pivotal role in the formation of the hemostatic plug. Platelets enhance clot strength by eightfold, relative to platelet-free fibrin clots seen on TEG. Platelet counts can be obtained in 30–40 min in the laboratory, but this provides only quantitative information. Thus, the qualitative and quantitative information on platelet function provided by TEG seems more timely (15 min) and practical.

The patients that we have described here required multiple blood products for hemostasis. Conventional blood product management has a long turn-around time: laboratory tests plus preparation of products by the blood bank. The bedside use of TEG enabled us to diagnose hemostatic abnormality and prepare blood products in a more timely manner. Lack of early detection of hemostatic abnormality and appropriate therapy can result in serious consequences: hemorrhage, and hemodynamic instability, followed by massive fluid transfusion. The latter may lead to significant hemodilution, worsening coagulation function. On the other hand, the administration of unnecessary hemostatic products may not only increase the risk of hypercoagulability but may also increase the chance of anaphylactic reactions or blood-borne infection. In our patients, the responses to blood products were monitored by repeated TEG, and we were able to guide our transfusion therapy. There was no indication of a hypercoagulable state. TEG is one of the coagulation tests that is useful

for reducing the consumption of blood products during surgery [2,4,5].

In summary, we would like to recommend the use of celite-activated TEG in high-risk surgical patients as a point-of-care coagulation monitor.

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