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Original contribution

Point-of-care viscoelastic testing improves the outcome of pregnancies complicated by severe postpartum hemorrhage

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1. Introduction

Postpartum hemorrhage (PPH)—defined as an estimated blood loss >500 mL following vaginal delivery and >1000 mL following cesarean [1,2]—is the leading cause of maternal mortality worldwide accounting for 27% of all maternal deaths, [3,4] and is the foremost cause of direct obstetric death in developed countries [5,6]. It is also a major cause of maternal morbidity and intensive care unit (ICU) admissions [7,8]. The incidence of PPH is increasing [9,10]. This is especially true of severe PPH, defined as an estimated blood loss in excess of 1500 mL [11,12]. Standardized hospital protocols have been developed in an effort to optimize the management of PPH and reduce peripartum morbidity and mortality [13,14]. These protocols generally follow the principles of empiric resuscitation, sometimes referred to as 'damage control resuscitation' [15]. Such protocols, developed initially in trauma medicine, deemphasizes crystalloid infusion in favor of early transfusion of high volumes of fresh frozen plasma (FFP), packed red blood cells (PRBC), and platelets without adjusting blood product transfusions to the results of coagulation tests [16–18]. The objective of these standardized protocols is to minimize dilutional and consumptive coagulopathy and avoid delay in blood product replacement in the setting of ongoing blood loss [19,20]. However, empiric resuscitation is not universally accepted [21].

It has been suggested that blood product resuscitation should be individualized and adjusted according to the results of point-of-care viscoelastic testing (PCVT). This approach has been shown to decrease morbidity and mortality among cardiac, [22,23] liver transplant, [24] and trauma patients [25,26] experiencing severe bleeding. In Europe, PCVT has been used also for the management of obstetric hemorrhage with good success [27,28]. To improve the care of patients with severe PPH, a standardized massive transfusion protocol based on empiric resuscitation principles was implemented on Labor & Delivery at Yale-New Haven Hospital in New Haven, CT in January 2011. Two years later, this was replaced by an individualized PCVT-guided transfusion management approach. The primary objective of this study was to compare clinical outcomes (specifically volume of transfused blood product, rate of volume overload, and rate of ICU admission) and hospital costs

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for patients with severe PPH managed with and without the PCVT-guided transfusion protocol in an historical cohort. We hypothesized that utilization of bedside thromboelastometry can improve clinical outcomes and decrease the cost of care by supporting accurate and clinically effective decisions in transfusion management in patients with severe PPH.

2. Materials and methods

A retrospective cohort study was conducted of consecutive patients with severe PPH managed on Labor & Delivery at Yale-New Haven Hospital in New Haven, CT between January 1, 2011 and July 31, 2015. The first day of the study corresponded with the date on which the massive hemorrhage protocol was introduced. This was replaced by the PCVT-based protocol on May 1, 2014. This study was approved by the Institutional Review Board of the Human Investigation Committee of the Yale University Human Research Protection Program.

The PPH management team included faculty members from obstetric anesthesiology, maternal-fetal medicine, and hematology. Specialists in Gynecologic Oncology were involved in some cases. Severe PPH was diagnosed if the estimated blood loss was 1500 mL or greater [2]. Patients were divided into two cohorts: (i) those where blood product transfusion was guided by PCVT, and (ii) those for whom PCVT was not available, which included all patients prior to May 1, 2014 and those after that date if personnel trained in PCVT were not immediately available. PCVT training included a structured didactic course, a practical hands-on session, skills testing, and subsequent certification. Only personnel who completed the training and received a certificate were allowed to perform PCVT and interpret results. PCVT-certified personnel were subject to Clinical Laboratory Improvement Amendments (CLIA) regulations, [29] which cover quality control rules, proficiency testing, and competency assessment criteria, which all were supervised by representatives of the Department of Laboratory Medicine at Yale-New Haven Hospital. If no PCVT-certified provider was available, the patient received empiric resuscitation according to the conventional protocol.

Viscoelastic testing was performed using a ROTEM *delta* device (Tem Innovations GmbH, Munich, Germany) in accordance with the recommendations of the manufacturer and interpreted by a trained anesthesiologist [30]. This training included didactics and practicum based on the PCVT protocol approved by the U.S. Food and Drug Administration, followed by a mandatory competency test [31,32]. Clinicians performed three separate analyses to assess the status of the patient's hemostatic cascade in the whole blood sample in real time, including: (i) clotting time and clot amplitude at a specific time after activation with tissue factor (EXTEM); (ii) an intrinsically activated test using ellagic acid (INTEM); and (iii) platelet inhibition with cytochalasin D (FIBTEM). Analysis was completed within 5 to 10 min of blood collection in all instances. All tests were performed at the bedside on Labor & Delivery at Yale-New Haven Hospital.

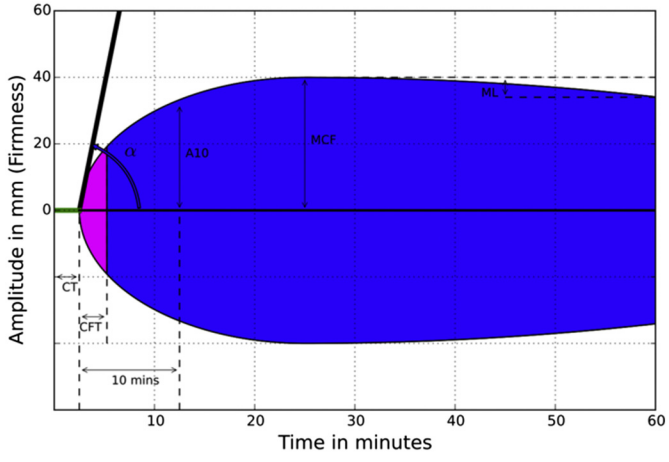

Fig. 1. Diagrammatic Representation of a TEMogram. CT, clotting time; CTF, clot formation time; A10, amplitude at 10 min; MCF, maximum clot firmness; ML, maximum lysis of the clot.

PCVT data are presented on a chart known as a TEMogram (Figs. 1 and 2). The TEMogram provides a graphic and digital representation of the blood clot that is formed after mixing the patient's whole blood with the prescribed reagent solutions and gently rotating the mixture. The clot movement pattern depiction on the TEMogram is generated by special sensors that reflect changes in the viscoelastic properties of the blood during rotation. The following key parameters were routinely analyzed:

(1) Clotting time (CT), which refers to the time elapsed from the beginning of the test until the beginning of clot formation. CT prolongation suggests a deficiency of one or more coagulation factors. CT prolongation only in EXTEM suggests a deficiency in coagulation factors in the extrinsic pathway (due, for example, to the effects of warfarin). CT prolongation only in INTEM is seen most commonly in patients receiving heparin or low-molecular weight heparin; a shortening of the CT in the HEPTEM assay confirms this effect.

(2) Clot formation time (CFT) refers to the time measured from the end of the CT interval until a 20 mm amplitude is reached on the TEMogram. Alpha angle describes the tangent at the 2 mm amplitude point. Both CFT and alpha angle reflect the speed of clot development. Prolonged CFT and/or low alpha angle are most often caused by one or more of the following conditions: thrombocytopenia, platelet dysfunction, hypofibrinogenemia, or dysfunctional fibrin polymerization.

(3) Maximum amplitude of the graph is measured either as an absolute parameter independent of time (maximum clot firmness [MCF]) or at a specific point in time after starting the test (e.g., A5 refers to maximum amplitude at 5 min, A10 refers to maximum amplitude at 10 min, etc.). This measurement reflects the functionality (strength) of the clot. As with CFT and alpha angle, a decrease in the maximum amplitude suggests one or more of the following conditions: thrombocytopenia, platelet dysfunction, hypofibrinogenemia, or dysfunctional fibrin polymerization.

(4) Maximum lysis (ML) refers to the percentage of lost firmness of the clot at a given point in time. It reflects a percentage of remaining clot firmness when compared with MCF at 30 min (LI30), 45 min (LI45), or 60 min (LI60). An abnormally high ML index suggests the presence of hyperfibrinolysis and is an indicator that antifibrinolytic therapy may be required.

Accurate interpretation of the TEMogram was a critical component of the decision making process, helping to guide blood product transfusion management in patients with severe PPH. Specifically, we used CT, CFT, alpha angle, MCF, and ML to guide blood products transfusion. The following parameters were considered normal for patients in the third trimester of pregnancy: (i) EXTEM: CT 51–63 s, CFT 70–78 s, and MCF 66–71 mm; (ii) INTEM: CT 131–168 s, CFT 58–66 s, and MCF 64–68 mm; and (iii) FIBTEM: CT 50–64 s and MCF 19–22 mm. [33,34] When the amplitude in the FIBTEM assay was <5 mm at 5 min (A5) or <6 mm at 10 min (A10), we administered 5 to 15 units of cryoprecipitate. The goal of the cryoprecipitate administration was to achieve an A10 of 8 mm for patients with surgically-controlled hemorrhage and 10 mm for patients with ongoing hemorrhage. We repeated the test at the end of the cryoprecipitate transfusion and every 20 to 60 min thereafter (depending on the patient's condition) until the bleeding was controlled. If the FIBTEM results were normal, but the CFT and alpha angle demonstrated hypocoagulation accompanied by a