Thromboelastography-Guided Blood Product Use Before Invasive Procedures in Cirrhosis With Severe Coagulopathy: A Randomized Controlled Trial

Jody C. Olson, M.D., F.A.C.P.

KEY POINTS

How will this study change day-to-day clinical practice?

- This study demonstrates the safety of viscoelastic testing as a tool to guide blood product replacement in patients with cirrhosis with abnormal standard tests of coagulation and will decrease the use of unnecessary blood product administration in this patient group.

What additional research questions are raised by this study?

- This study addresses abnormalities in only two TEG parameters and one set of transfusion threshold values.

Future studies should address different transfusion thresholds and the contribution of additional TEG parameters, such as α angle, LY30, and K time, to the management of coagulopathy.

Cirrhosis hospitalizations in the United States have approached 700,000 per year, with an annual cost to the US health care system of approximately \$12 billion.¹ These trends demand that cost-effective, evidence-based practices be used in caring for this population. One area of concern is the overuse of blood products in patients with cirrhosis who are undergoing invasive procedures. Patients with cirrhosis admitted to the hospital often require

Abbreviations: FFP, fresh frozen plasma; GPIIb/IIIa, glycoprotein IIb/IIIa; INR, international normalized ratio; MA, maximum amplitude; ROTEM, rotational elastometry; SOC, standard of care; TEG, thromboelastography.

From the Department of Medicine and Surgery, University of Kansas, Medical Center, Kansas City, KS.

Potential conflict of interest: Nothing to report.

Received June 15, 2018; accepted July 28, 2018.

View this article online at wileyonlinelibrary.com

© 2019 by the American Association for the Study of Liver Diseases

procedural intervention for management (e.g., endoscopy for assessment of gastrointestinal bleeding, diagnostic and therapeutic paracentesis). Patients with advanced liver disease frequently have significant abnormalities in standard tests of hemostasis, such as the prothrombin time, partial thromboplastin time, and platelet count, which are well recognized in the hepatology community. However, these abnormalities often provoke fear of increased bleeding risk in patients undergoing invasive procedures without a basis in evidence to justify such fear. This perception often leads to requests from procedural-based specialists for “correction” of coagulation test abnormalities, resulting in increased costs and risks for this patient population. Significant advances have been made in our understanding of hemostasis in liver disease. Our current understanding is that a rebalancing of hemostatic forces exists in patients with liver failure, resulting in a fragile but stable coagulation profile² (Table 1); in fact, patients with cirrhosis may tend toward a hypercoagulable state with risk for thromboembolism.³ Continued work in this area serves to dispel misunderstanding of the true hemostatic profile of the patient with cirrhosis.

In an effort to further advance the science of rational blood product usage in patients with cirrhosis undergoing invasive procedures, De Pietri and colleagues⁴ performed a randomized controlled trial evaluating the safety and efficacy of a viscoelastic testing procedure, thromboelastography (TEG), to guide blood product replacement in patients undergoing a variety of invasive procedures. In this study, a total of 60 patients with severe coagulopathy, as defined by an international normalized ratio (INR) greater than 1.8 and/or a platelet count less than $50 \times 10^9/L$, were randomized 1:1 to either TEG-guided blood product replacement or standard of care (SOC) (guided by INR and platelet count). Patients were excluded from the study on the basis

of active bleeding, thrombotic events, anticoagulant or antiplatelet therapy within 7 days of screening, presence of documented infection or sepsis, or hemodialysis within 7 days of screening.

Viscoelastic testing procedures include TEG and rotational elastometry (ROTEM), both of which are whole blood assays used to measure the evolution of clot structural development and the ability of the clot to perform its basic role in promoting hemostasis. This structural evolution is represented graphically in computer-generated tracings in real time (Fig. 1). In the TEG assay, the primary parameters measured include the R time, K time, α angle, the maximum amplitude (MA), the coagulation index, and LY30 (see Table 2 for an explanation of TEG parameters). Both TEG and ROTEM have been extensively used to guide blood product replacement in patients undergoing liver transplantation and cardiovascular surgery.^{5,6} Limited data exist on the use of TEG or ROTEM in the management of inpatients with cirrhosis undergoing invasive procedures. The findings of De Pietri et al.⁴ further our knowledge in this area.

Key findings in De Pietri et al.’s⁴ study were: (1) post-procedural bleeding events are indeed rare, and (2) TEG-guided blood product usage prior to invasive procedures results in a significant decrease in use of blood products without an associated increase in bleeding complications as compared with transfusion guided by the traditional measures of INR and platelet count. In this study, patients in the TEG arm received fresh frozen plasma (FFP) at a dose of 10 mL/kg ideal body weight if the R time was greater than 40 minutes, and platelets were administered when the MA was less than 30 mm. In the SOC group, patients were administered FFP at a dose of 10 mL/kg ideal body weight if the INR was greater than 1.8 and/or platelets if

TABLE 1. FEATURES OF COAGULATION IN LIVER DISEASE RESULTING IN A “REBALANCING” OF HEMOSTASIS

Hemostasis Stage	Hemostatic Forces Favoring Thrombosis	Hemostatic Forces Favoring Bleeding
Primary hemostasis: platelet interaction with vessel walls	<ul style="list-style-type: none">• Low levels of ADAMTS 13• Increased levels of von Willebrand factor	<ul style="list-style-type: none">• Thrombocytopenia
Secondary hemostasis: fibrin clot formation	<ul style="list-style-type: none">• Elevated levels of factor VIII• Decreased levels of proteins C and S, antithrombin, and heparin cofactor II	<ul style="list-style-type: none">• Low levels of factors II, V, VII, IX, X, and XI• Low levels of fibrinogen• Vitamin K deficiency (malabsorption in cholestatic disorders)
Fibrinolysis	<ul style="list-style-type: none">• Low plasminogen levels	<ul style="list-style-type: none">• Low levels of factor XIII and thrombin-activated fibrinolysis inhibitor• Elevated levels of tissue plasminogen activator

FIG 1 A normal TEG tracing. The typical parameters with the range of normal values are represented in this image. Red arrows have been drawn from the primary TEG parameters of interest to their corresponding feature on the tracing.

TABLE 2. TEG PARAMETERS AND CLINICAL IMPLICATIONS*

R time	Time of latency from the time the blood is placed in the reaction vessel until initial clot formation. Prolongation of R time suggests factor deficiency and may be corrected with FFP administration.
α angle	A measure of the kinetics of fibrin cross-linking or speed of clot strengthening. Low angle may suggest a deficiency in fibrinogen and is also influenced to a lesser extent by platelet number, and/or function may be corrected by administration of cryoprecipitate.
K time	The point at which the tracing reaches 20 mm of amplitude, a reflection of development of clot strength. With the α angle, K time is affected by the availability of fibrinogen. Prolongation of K time may be corrected by administration of cryoprecipitate.
MA	The MA is a direct function of the properties of fibrin and platelet bonding via (glycoprotein IIb/IIIa) GPIIb/IIIa and represents strength of the fibrin clot. The MA is affected by platelet number and function and, to a lesser extent, by fibrinogen levels. Low MA may be corrected by administration of platelets.
Coagulation index	A liner combination of the above parameters serving as a global view of the patient’s hemostatic profile.
LY30	Measure of rate of clot breakdown 30 minutes after MA. Hyperfibrinolysis may be corrected by aminocaproic acid (Amicar).

*This is meant to serve as a brief reference and not as a comprehensive tool for use of TEG for correction of hemostatic abnormalities. Correction of TEG abnormalities must occur in the appropriate clinical context.

the platelet count was less than $50 \times 10^9/L$. Five (16.7%) patients in the TEG group received blood products prior to planned procedures as compared with 30 (100%) patients in the SOC group ($P < 0.001$). Only one procedural-related bleeding event was reported across the entire cohort, and this occurred in the SOC group. Similarly, only one transfusion-related side effect was reported, also in the SOC group.

De Pietri et al.’s⁴ study supports previous findings regarding the INR: (1) The INR does not predict risk for procedure-related bleeding,⁷ and (2) administration of FFP does not necessarily correct INR or reduce bleeding events.^{8,9} There are clear limitations in utilization of the INR in assessment of bleeding risk in liver disease, a point that is often misunderstood.

Importantly, the work of De Pietri et al.⁴ clearly demonstrates that viscoelastic testing assays offer safe and rational guidance for blood product administration in patients undergoing invasive procedures. However, limitations to this study exist, notably its small size and exclusion of infected patients, who are particularly susceptible to increased abnormalities in hemostasis. Furthermore, this study addressed abnormalities in only two TEG parameters, R time and MA, and did not address the role of abnormalities in K time, α angle, or LY30, all of which may have important contributions to assessment and prevention of bleeding risk in advanced liver disease. Lastly, the study did not address differing “cutoff” values for blood product replacement; it is possible that an even more conservative approach may be equally as safe and result in even less blood product administration. Regardless, this is

an important study that serves to advance our understanding of management of bleeding risk in patients with cirrhosis who are undergoing invasive procedures and serves as a foundation for future studies in this area.

CORRESPONDENCE

Jody C. Olson, M.D., F.A.C.P., Associate Professor of Medicine and Surgery, University of Kansas Medical Center, 4000 Cambridge Circle, MS 1023, Kansas City, KS 66160. E-mail: jolson2@kumc.edu

REFERENCES

- 1) Allen AM, Kim WR, Moriarty JP, et al. Time trends in the health care burden and mortality of acute on chronic liver failure in the United States. *Hepatology* 2016;64:2165-2172.
- 2) Lisman T, Porte RJ. Rebalanced hemostasis in patients with liver disease: evidence and clinical consequences. *Blood* 2010;116:878-885.
- 3) Wu H, Nguyen GC. Liver cirrhosis is associated with venous thromboembolism among hospitalized patients in a nationwide US study. *Clin Gastroenterol Hepatol* 2010;8:800-805.

- 4) De Pietri L, Bianchini M, Montalti R, et al. Thromboelastography-guided blood product use before invasive procedures in cirrhosis with severe coagulopathy: a randomized, controlled trial. *Hepatology* 2016;63:566-573.
- 5) Alamo JM, Leon A, Mellado P, et al. Is "intra-operating room" thromboelastometry useful in liver transplantation? A case-control study in 303 patients. *Transplant Proc* 2013;45:3637-3639.
- 6) Shore-Lesserson L, Manspeizer HE, DePerio M, et al. Thromboelastography-guided transfusion algorithm reduces transfusions in complex cardiac surgery. *Anesth Analg* 1999;88:312-319.
- 7) Segal JB, Dzik WH. Paucity of studies to support that abnormal coagulation test results predict bleeding in the setting of invasive procedures: an evidence-based review. *Transfusion* 2005;45:1413-1425.
- 8) Stanworth SJ, Brunskill SJ, Hyde CJ, et al. Is fresh frozen plasma clinically effective? A systematic review of randomized controlled trials. *Br J Haematol* 2004;126:139-152.
- 9) Yang L, Stanworth S, Hopewell S, et al. Is fresh-frozen plasma clinically effective? An update of a systematic review of randomized controlled trials. *Transfusion* 2012;52:1673-1686; quiz.