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EDITORIAL

The Optimal Transfusion Strategy in Liver Transplantation: The Quest Continues

Nicolas M. Intagliata, Patrick G. Northup, Stephen H. Caldwell

Center for the Study of Coagulation in Liver Disease, University of Virginia, Charlottesville, Virginia, USA.

Smart, *et al.* Rotational Thromboelastometry or Conventional Coagulation Tests in Liver Transplantation: Comparing Blood Loss, Transfusions, and Cost. *Annals of Hepatology*.

The physiology of hemostasis in decompensated cirrhosis is profoundly distinct from any other disease state encountered during surgery. Our current understanding of the coagulation system in cirrhosis has expanded significantly over the last 15 years.[1,2] This new paradigm relies entirely on the concept of a rebalanced coagulation state, where all of the components of the system are significantly altered (both pro and anticoagulant portions), but maintained in a precarious equilibrium. External disruption of this balance, whether a consequence of disease progression or from human intervention, can thrust the balance into bleeding or thrombosis, often in dramatic fashion. Liver transplantation represents one of the greatest physiological insults to this balance. In the perioperative period, both bleeding or thrombosis can be catastrophic, which imbues a strong impulse to aim all measures at prevention. However, without an adequate measure to provide guidance, current efforts at prophylactic therapy are often misguided and potentially counter-productive. Particularly transfusion of large volumes of blood product (excessive use of fresh frozen plasma (FFP)) can only serve to potentiate portal hypertension and beget a vicious cycle of bleeding.[3,4]

Examination of the coagulation system is significantly limited by reliance on ex vivo testing, typically with isolation of plasma, protein and cellular components. By virtue of removing the blood from the patient, these tests omit important effects of endothelial interface interaction, signaling, and blood flow absent from the sterile confines of the test tube. The archetypal coagulation measure is the prothrombin time (PT) and international normalized ratio (INR), which test the speed at which the patient's plasma generates fibrin after artificial addition of tissue factor, phospholipids and calcium in a test tube. These tests do not accurately reflect the behavior of the coagulation system in cirrhosis[5] and while generally misleading, are often inappropriately applied to the bleeding 'forecast' and used as guides for prophylactic transfusion.

Viscoelastic tests (rotational thromboelastometry (ROTEM) and thromboelastography (TEG)) were developed to further assess some of these problems. Viscoelastic testing (VET) has been applied to liver transplantation as early as 1985 to assist in directing blood and factor transfusion to prevent or treat bleeding.[6] These tests use whole blood to measure the viscoelastic properties (shear strength of the clot) under movement of blood, mimicking in vivo conditions. Despite these early studies, the use of VET is not necessarily standardized and many institutions continue to rely on traditional measures of hemostasis, such as platelet level, PT/INR and factor levels. As more evidence accumulates, their successful application to liver transplantation is growing and published reports of suggested algorithms have emerged.[7,8]

In this edition of *Annals of Hepatology*, Smart, *et al*. report the results of a retrospective, single-center cohort study comparing the application of VET (ROTEM in this study) in the perioperative management of patients with cirrhosis undergoing liver transplantation. The authors compare past management of transfusion guided by traditional measures (platelet, PT/INR) of coagulation and compare this cohort to more recent transplant recipients managed with ROTEM guided transfusions. The authors note that there are significant limitations with the study design given the sample size and the possibility of bias from the evolution of surgical techniques and knowledge of

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coagulopathy management changing over time. Nonetheless, they found significantly reduced use of FFP in the group that was transplanted with ROTEM as a guide. Most importantly, they found that this group also had significantly reduced amount of blood loss. Perhaps as expected, by the nature of ROTEM, cryoprecipitate was used more frequently in the ROTEM group. ROTEM (via the simultaneous use of tests targeting different components of coagulation with EXTEM, INTEM, HEPTEM, FIBTEM and APTEM) allows users to parse out the contribution of specific components of the coagulation system, while testing in a whole blood sample.

The perceived advantage of VET is that testing occurs in whole blood, allowing visualization of potential nuances of the functional aspects of components of the coagulation cascade and the interaction of these components. This is not possible in standard testing of platelet level and INR. Cost is an important facet of medical care and imperative to understand when attempting to implement new technology aimed at shifting old and entrenched practice paradigms. VET requires the purchase of new machines, reagents and training of personnel. The authors took this into account and demonstrated an overall net decrease in costs with implementation of ROTEM. While the total cost saved was low and the study is not clearly powered to evaluated this, this finding is certainly encouraging and should pique the interest of transplant centers world-wide.

Global coagulation testing, such as VET, holds promise to aid in perioperative management of coagulopathy in liver transplantation. Certainly, any intervention to minimize the use of transfusions and decrease blood loss should be welcomed by the medical community. The possibility that VET may reduce overall costs is very attractive as well. However, we must remember major limitations and challenges to this field of study. First, patient populations with cirrhosis in general, and liver transplantation in particular, represent a widely heterogeneous group of patients, which makes application of standard transfusion algorithms difficult. Surgeon experience, anesthesia management and donor characteristics represent just a few of the numerous critical confounding variables that are unaccounted for in these studies. Second, while VET may represent a closer approximation of *in vivo* coagulation, it nonetheless remains an ex vivo study rife with artificial manipulation. While evidence is accumulating VET is an improvement on current testing, the results remain a human constructed "value" that cannot capture the true complex physiology that occurs in reality.

Transfusing plasma or providing medications to prevent future bleeding remains in the realm of educated guesswork in patients with cirrhosis undergoing procedures and liver transplantation. As our understanding of the coagulopathy in cirrhosis evolves, the argument for more reactive/restrictive strategies and minimization of unnecessary prophylactic transfusions, regardless if the target is INR, platelet level or VET output, seems much more appealing.[9] The quest for the "holy grail" in this field continues with the goal of finding a coagulation test that measures the entire system and provides continuous, immediate feedback to predict and prevent bleeding or clotting. While VET may move us a step closer to that goal, it is apparent that the quest continues.

ABBREVIATIONS

- **FFP:** fresh frozen plasma.
- **INR:** international normalized ratio.
- **PT:** prothrombin time.
- **ROTEM:** rotational thromboelastometry.
- **TEG:** thromboelastography.
- **VET:** viscoelastic testing

REFERENCES

1. Northup PG, Caldwell SH. Coagulation in liver disease: a guide for the clinician. *Clin Gastroenterol Hepatol* 2013; 11: 1064-74.
2. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. *N Engl J Med* 2011; 365: 147-56.
3. Massicotte L, Perrault MA, Denault AY, Klinck JR, Beaulieu D, Roy JD, Thibeault L, et al. Effects of phlebotomy and phenylephrine infusion on portal venous pressure and systemic hemodynamics during liver transplantation. *Transplantation* 2010; 89: 920-7.4. Zimmon DS, Kessler RE. The portal pressure-blood volume relationship in cirrhosis. *Gut* 1974; 15: 99-101.
5. Ewe K. Bleeding after liver biopsy does not correlate with indices of peripheral coagulation. *Dig Dis Sci* 1981; 26: 388-93.
6. Kang YG, Martin DJ, Marquez J, Lewis JH, Bontempo FA, Shaw BWJr, Starzl TE, et al. Intraoperative changes in blood coagulation and thrombelastographic monitoring in liver transplantation. *Anesth Analg* 1985; 64: 888-96.
7. Blasi A, Beltran J, Pereira A, Martinez-Palli G, Torrents A, Balust J, Zavala E, et al. An assessment of thromboelastometry to monitor blood coagulation and guide transfusion support in liver transplantation. *Transfusion* 2012; 52: 1989-98.
8. Roullet S, Freyburger G, Cruc M, Quinart A, Stecken L, Audy M, Chiche L, et al. Management of bleeding and transfusion during liver transplantation before and after the introduction of a rotational thromboelastometry-based algorithm. *Liver Transpl* 2015; 21: 169-79.
9. Intagliata NM, Caldwell SH, Porte RJ, Lisman T. Prediction of bleeding in cirrhosis patients: Is the forecast any clearer? *Hepatology* 2016; 64: 989-90.

Correspondence and reprint request:
Nicolas Intagliata, M.D.
PO Box 800708
Charlottesville, Virginia 22908-0708
E-mail: NMI4D@hscmail.mcc.virginia.edu