Understanding Coagulation and Hemostasis in Cirrhosis

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Hemostasis in cirrhosis

Patients with liver cirrhosis have altered hemodynamics and hemostatic pathways which may favor bleeding and at the same time may favor thrombosis. In stable cirrhosis, the system is rebalanced by off-setting factors.[1] Thrombocytopenia which is attributed to splenic sequestration and decreased thrombopoientin (TPO) is one of the most well-known anticoagulant change in liver cirrhosis. This anticoagulant change may be balanced by increased endothelial-derived von Willebrand factor (vWF).[2] Similarly, diminished liver derived procoagulant factors, such as factors V, VII, and X are offset by decreased liver-derived anti-coagulant factors, especially protein C.[3] However, this "rebalanced hemostasis" is precarious and may significantly be influenced by factors such as volume status, systemic infection and renal function. The hemostatic balance is much harder to maintain when the levels of the pro and anticoagulant factors are reduced by further deteriorated hepatic function, and the balance may be easily disrupted by the occurrence of stressful conditions such as infections and complications of liver cirrhosis.

Test of the coagulation system in cirrhosis

Currently available laboratory tests of the coagulation system are of limited value in estimating hemostatic competency in cirrhosis. Prothrombin time (PT), activated partial thromboplastin time (aPTT) and bleeding time (BT) are generally prolonged in patients with cirrhosis in accordance with the degree of hepatic decompensation. While these indices are useful for predicting prognosis in chronic liver disease, these tests perform poorly in assessing coagulation capacity in patients with liver disease.[4] International normalized ratio (INR) and PT reflect level of procoagulant factors I, II, V, VII and X, whereas do not measure the deficit of liver-derived anticoagulant factors such as protein C, and have a limitation in measuring in vivo activity of the coagulation system in cirrhosis.[5] Thrombocytopenia, while indirectly correlates with the degree of portal hypertension, may not necessarily indicates defect in thrombin generation since elevated vWF and increased circulating activated platelets may compensate the situation.[6]

Alternative means of assessing hemostatic pathway in cirrhosis have been suggested, but they are still for research use, and further development is required. The thrombin generation assay (TGA) measures the rate of production and decay of thrombin after introduction of a triggering agent such as tissue factor and phospholipid.[7] With addition of thrombomodulin, the integrity of the protein C anticoagulant system can also be assessed. However, TGA is not clinically available yet. Viscoelastic tests (VETs) measure clot strength and integrity in whole blood under low shear conditions to recreate the environment in vivo dur-

ing clot formation.[8] Although this may provide a more physiologic assessment of coagulation, VETs are not standardized in patients with cirrhosis and do not appear to predict bleeding of thrombosis objectively.

Coagulation assessment for invasive procedures

Despite the limitations of measuring platelet count and fibrinogen level in assessing hemostasis in cirrhosis, they are still the only tools for standard of care assessment of coagulation for all patients with cirrhosis when determination of values is indicated before a procedure.

Pre-procedure correction is recommended for high risk procedures. While there is no evidence that prophylactic platelet transfusion improves hemostatic potential,[9] current guidelines and expert opinion recommend considering platelet transfusion prior to high-risk procedures in patients with platelet counts below 50,000/uL.[10] Routing prophylaxis for low or moderate risk procedures is generally not recommended.[1] However, the prophylactic measures need to be individualized.

Table 1. Examples of procedure risk[11]

High risk procedures	Intermediate risk procedures	Low risk procedures
Brain or spinal surgery	Lumbar puncture	Paracentesis
Major surgery such as cardiac, intra-abdominal and orthopaedic surgery	Percutaneous or transjugular liver biopsy	Thoracentesis
Intra-cranial pressure catheter insertion	Transjugular intrahepatic portosystemic shunt	Dental extraction
Invasive endoscopy such as large polypectomy with endoscopic mucosal resection, natural orifice transluminal endoscopy	Endoscopy with moderate invasiveness such as percutaneous gastrostomy placement, cystgastrostomy, biliary sphincteerotomy	Endoscopy with lower invasiveness such as diagnostic variceal band ligation, uncomplicated polypectomy
	Percutaneous biopsy of extra-hepatic organ of lesions	Cardiac catheterization
	Trans-arterial or percutaneous HCC therapies	Central line plascement

Conclusions

The coagulation cascade is rebalanced in patients with cirrhosis, involving changes in both pro and anticoagulant factors. Although bleeding issues in cirrhotic patients have been recognized as the dominant clinical problems, inappropriate clotting has become more important as evidenced by the increased risk for both portal vein thrombosis (PVT) and venous thromboembolism (VTE).

References

1. O'Leary JG, Greenberg CS, Patton HM, Caldwell SH. AGA Clinical Practice Update: Coagulation in Cirrhosis. Gastroenterology 2019;157:34.
2. Lisman T, Bongers TN, Adelmeijer J, Janssen HLA, de Maat MPM, de Groot PG, et al. Elevated levels of von Willebrand factor in cirrhosis support platelet adhesion despite reduced functional capacity. Hepatology 2006;44:53-61.
3. Tripodi A, Primignani M, Lemma L, Chantarangkul V, Mannucci PM. Evidence that low protein C contributes to

the procoagulant imbalance in cirrhosis. Journal of Hepatology 2013;59:265-270.
4. Ewe K. Bleeding after Liver-Biopsy Does Not Correlate with Indexes of Peripheral Coagulation. Digestive Diseases and Sciences 1981;26:388-393.
5. Lisman T, Bakhtiari K, Pereboom ITA, Hendriks HGD, Meijers JCM, Porte RJ. Normal to increased thrombin generation in patients undergoing liver transplantation despite prolonged conventional coagulation tests. Journal of Hepatology 2010;52:355-361.
6. Giannini EG, Savarino V. Thrombocytopenia in liver disease. Current Opinion in Hematology 2008;15:473-480.
7. Hemker HC, Willems GM, Beguin S. A Computer-Assisted Method to Obtain the Prothrombin Activation Velocity in Whole Plasma Independent of Thrombin Decay Processes. Thrombosis and Haemostasis 1986;56:9-17.
8. Mallett SV. Clinical Utility of Viscoelastic Tests of Coagulation (TEG/ROTEM) in Patients with Liver Disease and during Liver Transplantation. Seminars in Thrombosis and Hemostasis 2015;41:527-537.
9. Tripodi A, Primignani M, Chantarangkul V, Lemma L, Jovani M, Rebulla P, et al. Global hemostasis tests in patients with cirrhosis before and after prophylactic platelet transfusion. Liver International 2013;33:362-367.
10. Northup PG, Caldwell SH. Coagulation in Liver Disease: A Guide for the Clinician. Clinical Gastroenterology and Hepatology 2013;11:1064-1074.
11. Intagliata NM, Argo CK, Stine JG, Lisman T, Caldwell SH, Violi F, et al. Concepts and Controversies in Haemostasis and Thrombosis Associated with Liver Disease: Proceedings of the 7th International Coagulation in Liver Disease Conference: October 6th and 7th, 2017 Rome, Italy. Thrombosis and Haemostasis 2018;118:1491-1506.