Assessing the Risk of Bleeding and Clotting in Cirrhosis

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Liver disease affects many organ systems including the hematological system responsible for bleeding and clotting. The high rate of hemorrhage has been previously recognized; however, the increased risk for thrombosis is only more recently being appreciated.¹ The complex interplay in liver disease can disrupt the prohemostatic and antihemostatic factors, thus leading to a disruption in the balance of bleeding and clotting in patients with chronic liver disease.² Assessment of true bleeding risk in this population is difficult, and often not accurate from the traditional measurement of singular values.

AN INADEQUATE MEASURE IN CIRRHOSIS: THE INTERNATIONAL NORMALIZED RATIO

The Protime/international normalized ratio (INR) is a traditional test for bleeding risk that was established by using the reference of patients on vitamin K antagonists. The use of this test was extrapolated to patients with liver disease. The measurement of Protime/INR occurs in platelet-poor plasma from serum, which essentially eliminates any interplay of these entities in clot formation. Moreover, it fails to detect protein C deficiency in cirrhosis, which dominates as a governor of thrombin and

hence fibrin generation. Also, cirrhosis-related interlaboratory variation in the INR values can cause significant variation in test results because of variable reagent activity.³ Nonetheless, some proceduralists will insist on arbitrary cutoffs for the INR and the administration of fresh frozen plasma, not understanding that each unit of fresh frozen plasma has very little effect on the actual bleeding risk of the patient.⁴ We recommend that the INR be used only as a prognostic marker (Model for End-Stage Liver Disease, among others), but not as a measure of bleeding risk in cirrhosis.

PLATELETS

Platelet values are also affected in chronic liver disease. Decreased production of thrombopoietin and splenic sequestration caused by portal hypertension will often cause thrombocytopenia. This value, when reported in the complete blood count, is a quantified calculation of the number of platelets in a serum sample. This does not take into account functionality, adhesion capacity, or the patient's ability to generate thrombin. Although severely low platelet numbers of less than 50,000 may confer a higher bleeding risk, levels between 50,000 and 100,000

Abbreviations: INR, international normalized ratio; ROTEM, thromboelastometry; TEG, thromboelastography.

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TABLE 1. COAGULATION TESTS AND CLINICAL UTILITY

Test	Advantages	Drawbacks	Clinical Utility
INR	Widely available Commonly recognized	Only measures procoagulant factors II, VII, IX, and X, but not deficiency of anticoagulant factors	Very limited utility because of variation depending on reagents used
Platelets	Widely available Commonly recognized	Measures quantity not quality of function	Level >50,000 seems to result in adequate thrombin production
Fibrinogen	Widely available	Does not account for dysfibrinogenemia. Optimal levels are not established	Level >100-120 is useful in guiding repletion with cryoprecipitate
Factor VIII	Differentiate DIC (low levels) versus cirrhosis-related coagulopathy (high levels) as bleeding cause	Overall impact of elevated levels not clearly evident but thought to contribute to procoagulant state	High level of activity suggests cirrhosis versus low activity level suggests DIC
TEG	Global coagulation measure Accounts for interplay of all components of whole blood	Only available in limited centers Difficult to interpret—learning curve is evident	Helps differentiate defect in bleeding/thrombosis mechanism from clotting curve
ROTEM	Global coagulation measure Accounts for interplay of all components of whole blood	Only available in limited centers Difficult to interpret—learning curve is evident	Helps differentiate defect in bleeding/thrombosis mechanism from clotting curve

Abbreviation: DIC, disseminated intravascular coagulation.

may actually still generate adequate thrombin to promote clotting.⁵ Further, reduced activity of ADAMTS 13, a protein responsible for cleaving/regulating von Willebrand Factor (vWF), can lead to elevated vWF levels that promote clot formation in patients with cirrhosis.⁶

FIBRINOGEN

Fibrinogen is an essential glycoprotein that is converted into a fibrin clot by the coagulation cascade. Measurement of this level can indicate whether substrate is present to allow for clot formation, because its absence would increase bleeding risk. Decreased levels of fibrinogen have been noted in almost 40% of patients with cirrhosis.⁷ Repletion through cryoprecipitate is believed to be essential when low fibrinogen is noted during episodes of hemorrhage.

OTHER FACTORS

Because protein C deficiency in cirrhosis is the key to rebalanced thrombin generation, measurement of this level perhaps along with factor VIII (typically elevated in cirrhosis) could theoretically provide an index of clotting potential. This approach, along with the more direct thrombin generation assay championed in key laboratory

studies by Tripodi and Mannucci² as means of assessing protein C activity, has not yet been adequately tested in the day-to-day ward setting to provide firm conclusions as to practical utility.

GLOBAL COAGULATION TOOLS

The tests mentioned earlier assess single components of the hemostatic profile for a patient. With so many factors affecting bleeding and clotting in liver disease, optimal bleeding or clotting determination is through global functional testing using whole blood samples from patients with cirrhosis. Thromboelastography (TEG) and thromboelastometry (ROTEM) have been shown to be effective in assessing clot formation and dissolution in the chronic liver disease population. These tests use whole blood to incorporate the interplay of the various serum components on clot formation. The whole blood is placed in cuvette, and the shear stress is measured from the solution on an inserted pin to determine clot formation. As clot is formed, the shear stress needed for rotation of the cuvette or pin also increases accordingly. Then, as the clot breaks down, the shear stress subsequently also decreases. TEG and ROTEM results and output curves were originally reported in the anesthesiology literature and are used in operating rooms, especially in

cases of liver transplantation. Administering these studies is often complicated, labor intensive, and has a steep learning curve for users, which promotes possible variation and inaccuracies. In general, their use seems to decrease blood product use as a result of reassurance of intact pathways.⁸

INDIRECT MEASURES OF BLEEDING RISK

Renal failure and infection are common complications and contribute to dysfunctional hemostatic pathways.^{9,10} Uremia can be associated with hypercoagulability measured by the global assays (see earlier). However, uremia is associated with defective platelet interaction leading to prolongation of the bleeding time. Infection is associated with release of endogenous heparinoids derived from the surface of the endothelium.¹¹ The effects are detectable with use of heparinase in performance of global clotting assays. In general, infection and renal failure are believed to contribute to a net bleeding diathesis in cirrhosis, and appropriate treatment is thought to decrease bleeding risk.

CONCLUSIONS

Our current tools for assessment of hemostatic profiles in patients with cirrhosis are evolving (Table 1). Used in combination, they may provide some insight into the risk for bleeding or clotting. Current global functional measures have promise but also have many steps, which increase the risk for human error, and provide complicated output results that require interpretation but often provide reassurance of intact systems. No singular approach will fit all individual patients. A combination of rational test assessments discussed earlier, including specific measures, as well as the patient's history and the context (presence of renal failure, infection, or both), can help to guide optimization of the hemostatic system.

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