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ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: If a patient has cirrhosis, should I correct coagulation abnormalities before a minor invasive procedure?

A 56-year-old man with a history of cirrhosis is hospitalized with decompensated liver cirrhosis, ascites, and encephalopathy. His hemoglobin is 9 g/dL (reference range 13.8–17.2), platelet count 40 × 10^9/L (150–400), and international normalized ratio (INR) 2.5 (0.8–1.1). Do I need to correct the patient's elevated INR or thrombocytopenia before performing diagnostic and therapeutic paracentesis?

A: No. An elevated INR in patients with cirrhosis does not predict the risk of postprocedural bleeding, and no evidence suggests that correcting a prolonged INR with fresh frozen plasma will lower procedure-related bleeding.[1] Transfusion of platelets to prevent bleeding in the setting of stable cirrhosis is not recommended for patients undergoing low-risk procedures such as paracentesis, thoracentesis, and liver biopsy.[1,2]

BLEEDING RISK WITH CIRRHOSIS: A TENUOUS BALANCE

In patients with cirrhosis, hemostatic system abnormalities are common and include thrombocytopenia, prolonged prothrombin time, prolonged activated partial thromboplastin time, elevated INR, and decreased fibrinogen. These abnormalities were once implicated in increased bleeding events, but it is now understood that changes in both prohemostatic and antihemostatic pathways contribute to a "rebalanced" hemostatic state,[3] and because this balance is tenuous, patients with liver disease are also susceptible to thrombotic events.[1]

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Prothrombin time, activated partial thromboplastin time, and INR are often elevated in the setting of cirrhosis because of low levels of coagulation factors produced by the liver and a concomitant decline in levels of protein C, protein S, and antithrombin.[3] The INR is one component of the Model for End-Stage Liver Disease score,[4] a commonly used prognostic model for cirrhosis. However, INR measurement, originally developed to standardize the prothrombin time for patients on warfarin, does not accurately reflect the hemostatic profile in patients with cirrhosis who are not taking warfarin.[5] A meta-analysis of 29 studies demonstrated no significant association between periprocedural bleeding events and preprocedural INR.[5]

Thrombocytopenia is a common consequence of hypersplenism and decreased hepatic thrombopoietin production, but the bleeding risk may be balanced by elevated levels of von Willebrand factor; by decreased levels of ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13), a potent inhibitor of von Willebrand factor; and by platelet activation by endotoxemia.[3] There is no consistent association between thrombocytopenia and risk of bleeding in patients with cirrhosis who undergo low-risk procedures.[1]

Studies have identified an association between severe thrombocytopenia (a platelet count less than 50 × 10^9/L) and bleeding after percutaneous liver biopsy, dental extractions, percutaneous ablation of liver tumors, and endoscopic polypectomy, but the results of these studies were likely confounded by the use of prophylactic platelet transfusions.[6] The risk of bleeding in patients with cirrhosis is determined by clinical and procedural factors unrelated to

coagulation testing. Anemia, renal failure, and sepsis are known clinical predictors of bleeding in this population.[1,3]

Invasive procedures are classified as having a low or high risk of bleeding, with low bleeding risk defined as a bleeding rate less than 1.5%. Procedures associated with low bleeding risk include paracentesis, thoracentesis, liver biopsy, and percutaneous ablation of liver cancer.[1] Ultrasonographic guidance has been shown to reduce bleeding complications in certain procedures, most notably placement of a central line in patients with coagulopathy.[1]

WHAT DO GUIDELINES RECOMMEND?

For patients with cirrhosis, current guidelines recommend a conservative approach to prolonged INR, thrombocytopenia, and fibrinogen deficiency.

Prolonged INR: Avoid fresh frozen plasma

Correction of prolonged INR with fresh frozen plasma to decrease procedure-related bleeding is not recommended in the European Association for the Study of Liver clinical practice guidelines on bleeding and thrombosis in patients with cirrhosis.[1] In a combined retrospective and prospective study of 100 patients, Yousef et al[7] found that fresh frozen plasma transfusion corrected prothrombin time in only 12.5% of patients in the retrospective groups and 10% of patients in the prospective groups. A Cochrane review on the use of prophylactic fresh frozen plasma demonstrated no benefit in procedure-related bleeding in patients with cirrhosis.[8] Possible consequences of fresh frozen plasma transfusion include increased portal hypertension as a result of increased blood volume, transfusion-associated circulatory overload, transfusion-related acute lung injury, and allergic or anaphylactic reactions. Given the risks, transfusion of fresh frozen plasma to correct prolonged INR in cirrhosis should be avoided.[1]

Thrombocytopenia: Case-by-case decision

Studies that evaluate the efficacy of platelet transfusion or thrombopoietin receptor agonists to prevent bleeding in patients with cirrhosis are lacking. The American Gastroenterological Association recommends against routine use of platelet transfusions or thrombopoietin receptor agonists for procedures such as paracentesis, thoracentesis, variceal banding, colonic polypectomy, endoscopic retrograde cholangiopancreatography, and liver biopsy.[2]

In vitro studies have established that in patients who have cirrhosis and platelet counts greater than 56×10^9/L, platelet-dependent thrombin formation is preserved.[1,9] This finding is the theoretical basis for guidelines that recommend avoidance of platelet transfusion or thrombopoietin receptor agonists when the platelet count is greater than 50×10^9/L. In patients with platelet counts less than or equal to 50×10^9/L who are undergoing a high-risk procedure (eg, endoscopic retrograde cholangiopancreatography, endoscopic polypectomy, ligation of esophageal varices), transfusion of thrombopoietin receptor agonists may be considered on a case-by-case basis,[1] and decisions can be made with the guidance of a hepatologist or a hematologist. Additional prospective studies are needed to determine the efficacy of platelet transfusion or thrombopoietin receptor agonists to prevent bleeding in patients with cirrhosis.

Fibrinogen deficiency: Routine correction not recommended

Fibrinogen is necessary for clot formation and can be increased by administration of cryoprecipitate. Although fibrinogen levels below 100 mg/dL are associated with bleeding in patients with cirrhosis, this association may reflect the severity of disease rather than a cause.[1,10] A retrospective study evaluating the effect of cryoprecipitate transfusion for critically ill patients with cirrhosis and hypofibrinogenemia failed to demonstrate reduced bleeding with routine cryoprecipitate transfusions.[7,11] Given the lack of evidence that cryoprecipitate transfusion prevents bleeding and avoids the high cost of cryoprecipitate, routine correction of fibrinogen deficiency to prevent procedure-related bleeding is not recommended.[1]

Viscoelastic testing: Unsupported in nonsurgical settings

Thromboelastography and rotational thromboelastometry are types of viscoelastic testing (VET) that evaluate the rate, stability, and strength of blood clot formation and the rate of dissolution in whole blood.[12] VET is thought to represent in vivo hemostasis better than more traditional coagulation testing such as INR, prothrombin time, and activated partial thromboplastin time. Used routinely during liver transplant surgery, VET is associated with decreased use of blood products without an increase in bleeding adverse events.[12] The strategy is increasingly favored for evaluation of coagulopathy in cirrhosis because of unclear benefit associated with following and correcting traditional coagulation markers such as INR.

In a meta-analysis, Shenoy et al[12] compared standard of care based on platelet and INR guidelines

vs VET-guided preprocedural transfusions. In the VET group, 14.4% required platelet transfusions and 22.2% required fresh frozen plasma, compared with 64.7% and 55.6% in the standard-of-care group. Decreased preprocedural transfusions in the VET group did not result in increased postprocedural bleeding events or mortality.[12] However, the analysis was unable to define common VET-based transfusion thresholds among the studies included. The authors recommended against the use of VET in patients with cirrhosis undergoing nonsurgical procedures such as paracentesis, thoracentesis, or liver biopsy, citing limited availability of the technology and specialized training required to use it.

THE BOTTOM LINE: MORE STUDIES NEEDED

Because of rebalanced hemostasis, traditional laboratory testing such as prothrombin time, activated partial prothrombin time, INR, and platelet counts are unhelpful in predicting the risk of bleeding in cirrhosis. Studies have demonstrated that correction of INR with fresh frozen plasma in this patient population is often ineffective in normalizing the INR and preventing postprocedural bleeding.[11] The threshold level of thrombocytopenia at which platelet transfusions and thrombopoietin receptor agonists are beneficial in cirrhosis is unknown. Similarly, the cutoff for transfusion of cryoprecipitate for decreased fibrinogen levels has not been elucidated, and routine administration of cryoprecipitate for prevention of postprocedural bleeding is not recommended.[1]

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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