ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Management of Coagulopathy in Liver Disease

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G&H Where are we in understanding the pathogenesis of coagulopathy in patients with liver disease?

SC In the past, it was generally thought that the prolonged prothrombin time in patients with liver disease reflected a bleeding tendency. It has become clear over the past few years, though, that, although a bleeding tendency exists, so does a clotting tendency. Neither the bleeding nor clotting tendency is well measured by the conventional prothrombin time or the related international normalized ratio (INR). The reasons are complex and multifactorial, but several processes are rebalanced in a patient with cirrhosis who is stable, resulting in hemostatic equilibrium. Decompensation, worsening portal hypertension, renal failure, and infection can place the patient at greater risk for bleeding. On the other hand, the anticoagulant system that is normally present and balances clotting is also deranged in liver disease, resulting in a very low protein C level. That together with increases in factors produced in the endothelium of the blood vessels, such as factor VIII and von Willebrand factor, lead to a relative hypercoagulable state. Coupled with relative venous stasis in cirrhosis, especially in the portal vein but also peripherally, inappropriate clot formation can result.

G&H What is the relationship between hyperfibrinolysis and coagulopathy?

SC Hyperfibrinolysis is one of the several conditions that are superimposed onto liver disease–related coagulopathy. Hyperfibrinolysis is difficult to measure, and its presence remains controversial probably because of the different methods used by different laboratories to detect it. However, it is one of the oldest disturbances described in patients with liver disease. Going back to the early 1900s, Dr Ernest W. Goodpasture (1886-1960) famously described early clot lysis and rapid clot lysis in liver disease. Moving ahead 100 years from that time, it is apparent that premature clot lysis is present in some patients but still not well understood. It is estimated that between 5% and 10% of patients with decompensated cirrhosis will have clinical evidence of hyperfibrinolysis. The presence of hyperfibrinolysis means that the patient will form a clot, but then the anticoagulant system kicks in and prematurely dissolves the clot. Hyperfibrinolysis should be suspected in patients with mucosal bleeding, oozing from puncture sites, or late bleeding after a procedure in which a patient appears stable at first and then experiences bleeding a few hours later. Body cavities, such as the mouth after dental extractions, the biliary tree after liver biopsy, and the bladder, are especially prone to hyperfibrinolysis because they contain fibrinolytic substances. It is particularly important to recognize those at risk because antifibrinolytic agents, such as aminocaproic acid (Amicar, Clover Pharmaceutical Corp), can be used therapeutically.

G&H How is hyperfibrinolysis diagnosed?

SC Hyperfibrinolysis is currently still a largely clinical diagnosis and should be considered in any patient with liver disease and bleeding. Laboratory tests to detect hyperfibrinolysis are not readily available, although there

are several of them. A low fibrinogen measure may be a signal that a component of hyperfibrinolysis is present. Examination of clot lysis times and thromboelastography are a little more cumbersome and not available in all centers, but these can be helpful.

The diagnosis of hyperfibrinolysis is often based on a constellation of findings, and there is not one specific, widely available test to nail it down. A team of investigators and I at the University of Virginia are studying a device that might help, but outcomes will not be available for several years at best.

G&H How prevalent are bleeding and thrombotic complications in cirrhosis?

SC Bleeding events are more common than clotting events among hospitalized patients and patients with decompensated cirrhosis. The risk of postprocedure bleeding for so-called minimally invasive procedures is about 20%, which is why anyone conducting procedures in patients with liver disease will be concerned about their bleeding risk. In the past, the effort was aimed at correcting the prothrombin time and/or the INR. We now know that the prothrombin time test and INR only measure the procoagulant pathway and do not detect the defects in the anticoagulant pathway. Targeting the INR or the prothrombin time alone leads to unnecessary volume expansion and especially overuse of plasma. For each 100 cc of plasma infused, the portal pressure goes up about 1 mm of mercury. This, of course, can cause a significant increase in portal hypertension and engorgement of collateral vessels, such as varices and smaller vessels in mucosal surfaces such as the peritoneum. So we discourage use of prothrombin time or INR as a means of risk stratification among patients with liver disease who are going to have a procedure because the data that prothrombin time or INR provides are weak and because an inappropriate response, such as plasma infusion, can cause unintended complications.

We are developing an approach that focuses on more grounded measures, such as targeting the platelet count to be over 50,000 µL. A platelet level that is over about 50,000 µL is associated with improved thrombin production. As a corollary to that, we aim to have the fibrinogen level over 120 mg/dL because fibrinogen is the main target of thrombin and a final step in clot formation. If a patient is producing enough thrombin and has enough fibrinogen, then he or she should be able to form an adequate clot. The clinical data to support this strategy are very limited, but there is a sound rationale for the approach based on what we already know, and it offers a rational approach pending completion of clinical studies. We also try to do a bleeding risk assessment in which the patient is questioned about whether he or she bleeds easily, such as when shaving or brushing teeth, or whether he or she bruises easily or has nosebleeds. This kind of information can shed light on whether that patient has a defect that warrants prophylaxis. We also will look at renal function, which we will try to optimize, and signs of infection, which we will try to correct.

G&H What is the current thinking on vitamin K replacement?

SC We routinely use vitamin K supplementation, especially if we suspect a vitamin K deficiency, but vitamin K replacement usually has a minimal effect. The thinking has been that "it does not hurt and may help," so there is no harm in adding vitamin K supplementation to the treatment program.

G&H What is the role of antifibrinolytic agents in the treatment of cirrhosis? What precautions need to be taken to help prevent thrombosis?

SC We have treated a fair number of patients with antifibrinolytic agents and with aminocaproic acid, in particular, and I am not aware of an instance of having had a problem related to clot formation. Generally, aminocaproic acid has been fairly well tolerated, and there is literature to support its relative safety in patients with liver disease. Antifibrinolytics and other procoagulants, however, all carry the risk of thrombosis, and so they are used with caution. We counsel the patient and family that use of such treatments comes with a risk of development of a clot.

G&H Can you speak about the place of prothrombin complex concentrate in coagulopathy prophylaxis?

SC Because of the limited amount of actual clinical data, prothrombin complex concentrate is in about the same category as recombinant activated factor VII as perhaps a top rescue agent. For postprocedural bleeding that is thought to not be related to a hyperfibrinolytic process and for which urgent control is needed, recombinant activated factor VII is sometimes used, albeit with little supporting data, as a rescue agent. Because it does carry a risk of thrombosis and thrombotic complications, we reserve it for very extreme situations and then use it very cautiously.

As for prothrombin complex concentrate, European studies indicate that it is relatively safe, but it probably carries some hypercoagulable risk. To my knowledge, optimal dosing of prothrombin complex concentrate has not been adequately defined in patients with liver disease. More clinical testing is needed. The agent is marketed by

CSL Behring as Beriplex in Europe and Kcentra in the United States. At my institution, it is on the formulary for use by the hepatology group and is used, with caution, instead of factor VII. It consists of prothrombin factor II, VII, IX, and X and proteins C and S. It is very low volume, and it does affect the prothrombin time. I am not aware of any studies other than a European study that indicated relative safety. Although very promising, prothrombin complex concentrate has yet to be adequately investigated in these patients to provide firm guidance on how to deploy this new tool.

G&H What are the next steps regarding research?

SC The goal now is to do more translational work and further address the provocative questions that you raise. An elegant controlled trial was conducted by Stanca and colleagues that involved dental extractions in patients with cirrhosis in which the procoagulant desmopressin acetate (as DDAVP) was compared with blood products. Slightly better results were found with desmopressin, and it was a fraction of the cost and also very convenient to use because cross-matching and other requirements of blood product use are not needed. In light of the findings, we have incorporated use of intranasal DDAVP into our approach. If a patient is suspected of being at a particularly high risk of coagulopathy, we will recommend administration of a small dose of DDAVP about 45 minutes before the patient undergoes a procedure in addition to the general measures mentioned already, such as increasing platelet levels to over 50,000 µL and fibrinogen levels to 120 mg/dL or more, optimizing renal function as much as possible, and treating any coexisting infection. However, additional studies are needed to further assess risk stratification. It is likely that some patients with particularly hypercoagulable profiles, such as very low protein C and high factor VIII, require no prophylactic intervention but rather would benefit by emphasizing "rescue" measures should they have bleeding as a result of therapeutic or diagnostic tests.

Dr Caldwell has no relevant conflicts of interest to disclose.

Suggested Reading

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