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Original Articles

Hemostasis in Liver Disease: Implications of New Concepts for Perioperative Management

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ABSTRACT

The hemostatic profile of patients with liver diseases is frequently profoundly different from that of healthy individuals. These complex alterations lead to abnormal results from routine laboratory tests, but because of the nature of these assays, they fail to accurately represent the patient's hemostatic state. Nevertheless, based on abnormal laboratory coagulation values, it has long been assumed that patients with liver disease have a natural bleeding tendency and are protected from thrombosis. This assumption is false; the average patient with liver disease is actually in a state of "rebalanced hemostasis" that can relatively easily be tipped toward both bleeding and thrombosis. The new paradigm of rebalanced hemostasis has strong implications for the clinic, which are presented in this review. There is no evidence that prophylactic transfusion of plasma helps to prevent procedure-related bleeding. In addition, the presence of independent risk factors such as poor kidney status or infections should be carefully assessed before invasive procedures. Furthermore, central venous pressure plays an important role in the risk of bleeding in patients with liver diseases, so during procedures, a restrictive infusion policy should be applied. Finally, thrombosis prophylaxis should not be withheld from patients with cirrhosis or acute liver failure, and clinicians should be alert to the possibility of thrombosis occurring in these patients.

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Chronic liver disease and acute liver failure are associated with considerable changes of the hemostatic profile [1]. Historically, these changes were interpreted as predisposing for a bleeding tendency, and patients often received prophylactic transfusion of blood products prior to invasive procedures with the aim of reducing the bleeding risk. Developments in the care of liver transplant recipients, combined with experimental laboratory studies, have introduced new concepts with regard to the management of hemostatis in patients with chronic and acute liver disease. In brief, routine laboratory coagulation tests cannot predict bleeding risk, and prophylactic use of blood products

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may paradoxically contribute to bleeding rather than prevent it. These new insights have brought about a reduction in the use of blood products in patients undergoing liver transplantation. More and more centers report transfusion-free liver transplantation in a substantial proportion of patients [2]. These developments have profound implications for the general treatment policy for patients with liver disease who need to undergo an invasive procedure. Although avoidance of correction of the laboratory coagulopathy prior to surgery has been established in liver transplantation practice, the old dogma of prophylactic blood product transfusion guided by laboratory testing prior to other, less major invasive procedures still prevails [3,4]. This article reviews the developments in liver transplant surgery with regard to the management of hemostasis in patients with liver disease. In addition, we provide guidelines for the application of these newer insights in the management of hemostasis in patients with liver disease undergoing other invasive procedures.

The Hemostatic Profile of Patients With Liver Disease

The liver plays a central role in hemostasis as it synthesizes nearly all circulating coagulation factors and inhibitors, as well as some of the components of the fibrinolytic system. In addition, the liver synthesizes thrombopoeitin, which is a hormone essential for stimulation of platelet production from megakaryocytes in the bone marrow. Therefore, liver diseases (whether acute or chronic) frequently are associated with complex alterations of the hemostatic system. The typical hemostatic profile of patients with advanced liver disease consists of significantly decreased levels of nearly all proteins that promote or inhibit coagulation and fibrinolysis, thrombocytopenia, and platelet function defects. The reduced plasma levels of coagulation proteins can be directly explained from the loss of function of the failing liver but may also be a reflection of ongoing low-grade intravascular or intrahepatic activation of coagulation [5–7]. In contrast to most hemostatic proteins, levels of von Willebrand factor (VWF) are elevated, which could be due to enhanced production by the endothelium or reduced clearance by the liver. These elevated VWF levels may also be part of a compensatory mechanism that aids primary hemostasis [8]. Plasma levels of factor VIII are also substantially increased, which could be explained by physiological synthesis in other organs, which may be up-regulated in patients with liver failure [9,10]. The increased levels of factor VIII may be related to the elevation of its carrier protein VWF. Many patients with chronic liver diseases have portal hypertension and splenomegaly, which respectively leads to alterations in hemodynamics and increased platelet sequestration [11,12]. Results from routine laboratory tests like the prothrombin time (PT), its standardized variant international normalized ratio (INR), and activated partial thromboplastin time (APTT) are frequently prolonged [13]. In addition, patients with cirrhosis may have laboratory features of accelerated fibrinolysis, although this is debated [14,15]. In contrast, patients with acute liver failure present with laboratory features of inhibited fibrinolysis [16].

Although different etiologies of liver failure share the same general hemostatic pattern, there are notable differences between different types of liver disease. In cholestatic liver diseases, including primary sclerosing cholangitis and primary biliary cirrhosis, the hemostatic changes seem to be less pronounced as compared with patients with parenchymal disease [17,18]. In addition, patients with nonalcoholic fatty liver disease, a disorder with increasing prevalence in conjunction with the rise of obesity prevalence [19,20], are relatively prothrombotic reflected in the high incidence of thrombosis [21,22]. In patients with acute liver failure, thrombocytopenia is less common than chronic liver disease. The decrease in procoagulant and anticoagulant plasma factors, however, is generally more pronounced in acute than in chronic liver failure [21,23], and the average INR is higher [24].

Rebalanced Hemostasis

The classical interpretation of the hemostatic profile in patients with liver disease was that these patients have a bleeding tendency. This was believed to be supported by the abnormal laboratory coagulation test results and the observation that spontaneous bleeding occurs frequently in this group of patients. Furthermore, the fact that liver transplant recipients frequently required massive amounts of blood products during the procedure was also considered evidence of an existing bleeding tendency. This led to the clinical practice of preprocedural prophylactic correction of the platelet count, PT, and APTT through transfusion of blood components, with the assumption that this would help prevent intraoperative bleeding [3,4]. The types of transfusions that are frequently used include fresh-frozen plasma, platelet concentrates, cryoprecipate (or fibrinogen concentrate), packed red blood cell (RBCs), and/or whole blood. In line with this paradigm, patients were considered to be "auto-anticoagulated" and thromboprophylaxis was frequently withheld.

After several authors had pointed out the shortcomings of this classical interpretation of the coagulopathy of liver disease [5,6,25,26], we proposed the concept of "rebalanced hemostasis" [27]. In healthy individuals, hemostasis is in a solid balance between procoagulant and anticoagulant factors, thereby preventing bleeding or thrombosis. Both procoagulant and anticoagulant drivers are lowered in patients with liver disease, or compensatory mechanisms for hemostatic defects exist. Specifically, thrombocytopenia and platelet function defects are compensated (at least in part) by elevated levels of VWF, and coagulation and fibrinolysis are in a rebalanced status because of a concomitant decline in activators and inhibitors [27]. This rebalanced status is not reflected by the routinely performed hemostatic tests (platelet count, PT, APTT). Because the platelet count does not take the elevated VWF levels into account and because the PT and APTT are only sensitive for procoagulant proteins, they fail to reflect the polyfactorial changes in the hemostatic profile of patients with liver disease. Although spontaneous bleeding frequently occurs in patients with liver disease, in most cases, these are variceal bleedings that are caused by local vascular deformations and hemodynamic changes rather than coagulopathy. Furthermore, thrombotic complications also frequently occur in patients with liver disease (see later section for details), which would be unlikely, if not impossible, if patients were really "auto-anticoagulated." Finally, in the present-day practice of liver transplantation, a large proportion of patients are successfully operated on without the need of any blood transfusion [2,28]. If liver disease caused "true" coagulopathy, as observed in conditions such as hemophilia, this would likely not be possible [21].

The Limitations of PT and APTT and the Potential of Thrombin Generation Assays

The PT has been developed as a tool to diagnose defects or deficiencies in individual procoagulant proteins and to evaluate patients using vitamin K antagonist therapy [26]. However, the PT has been adopted as a general indicator of coagulation in a broad range of patients. Because of the nature of the assays, the PT and APTT cannot predict the risk of bleeding in patients with complex hemostatic alterations such as observed in liver disease [26,29–32]. The main reason for this is that these tests are insensitive to plasma levels of the anticoagulant pillars of hemostasis, that is, the protein C pathway, antithrombin, and tissue factor pathway inhibitor. In addition, these tests do not take the role of the endothelium in the hemostatic process into account. The PT only assays the function of a discrete number of procoagulant proteins (factors VII, X, V, and II and fibrinogen) and therefore cannot reflect the true hemostatic status of a patient.

In recent years, the thrombin generation test, which may more accurately reflect the status of the hemostatic system, has gained interest. In this test, the total amount of thrombin generated during in vitro coagulation is measured, which contrasts with the PT and APTT,