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Value of Preoperative Hemostasis Testing in Patients with Liver Disease for Perioperative Hemostatic Management

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DURING the preoperative workup of any patient undergoing moderate to major invasive surgery, an assessment of bleeding risk may be performed, but the role of laboratory testing is controversial.

Preoperative Hemostasis Testing

The United Kingdom National Institute for Health and Care Excellence (NICE) recommends consideration of laboratory tests of hemostasis in selected patients undergoing moderate or severe surgery and with an American Society of Anesthesiologists (ASA) physical status classification system score of 3 or 4.¹ The guideline specifically states to consider preoperative hemostasis testing in patients with chronic liver disease and ASA score of 3 or 4. The Practice Advisory for Preanesthesia Evaluation by the ASA² states that “clinical characteristics to consider for ordering selected coagulation studies include bleeding disorders, renal dysfunction, liver dysfunction, and type and invasiveness of procedure.” Routine preoperative hemostasis testing may include platelet count, prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen levels, although the NICE guidelines specifically refer to PT and aPTT testing only.

Patients with liver diseases frequently have abnormal routine diagnostic tests of hemostasis. It has long been a “common practice” to attempt to correct these abnormalities by transfusion of blood products before invasive procedures, but recent insights in the hemostatic status of patients with liver disease cast doubt on this policy.³ Specifically, routine laboratory values in patients with liver disease may not accurately reflect the hemostatic status of these patients,^{4,5} and

there is little evidence that routine preoperative hemostasis tests predict the risk for procedural bleeding in patients with liver disease.^{6–8}

In this commentary, we provide evidence that, in contrast to what is suggested by the NICE and ASA guidelines, the role of preoperative hemostasis screening for any patient with liver disease undergoing surgery is limited, which has important consequences for perioperative hemostatic management.

The Complex Coagulopathy of Patients with Liver Diseases

The liver is the site of synthesis of many proteins involved in hemostasis. Consequently, unique alterations in the hemostatic system frequently accompany chronic and acute liver diseases. Specifically, patients with liver diseases may develop thrombocytopenia and platelet function defects, decreased levels of pro- and anticoagulant proteins, and decreased levels of proteins involved in fibrinolysis. These changes frequently result in alterations in hemostasis screening tests such as the platelet count, PT, aPTT, and fibrinogen levels. A patient with liver disease and thrombocytopenia and/or prolongations in PT and/or aPTT has long been considered to have a hemostasis-related bleeding tendency. Clinical confirmation for the dogma that patients with liver disease have a bleeding diathesis was provided by the substantial perioperative blood loss during major surgical procedures (*i.e.*, liver transplantation)⁹ and the high frequency of gastrointestinal bleeding episodes. The notion that patients with liver disease have a hemostasis-related bleeding tendency led to the common practice of

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prophylactic transfusion of blood products before invasive procedures in those patients with liver disease and thrombocytopenia or prolongations in the PT and/or aPTT. We will argue that this approach is not evidenced-based, in most instances not required, and possibly harmful.

How Should Abnormal Coagulation Tests in Patients with Liver Disease be Interpreted?

Thrombocytopenia

Thrombocytopenia is common in chronic and acute liver failure and platelet function as assessed by suspension aggregometry, PFA-100 (Siemens Healthcare, Germany), or multiplate is decreased.¹⁰ *In vitro* analyses, however, show that the highly elevated levels of the plasma protein von Willebrand factor compensate for the low platelet count.^{4,11} In addition, there are studies that suggest platelet function *in vivo* is actually enhanced in patients with cirrhosis.¹² The thrombocytopenia of liver disease thus should be considered in the context of elevated von Willebrand factor levels and should not be interpreted in the same way as an isolated thrombocytopenia in an individual with normal liver function.

Prolonged PT and aPTT

Prolongations of the PT and/or aPTT are also common and are related to defects or deficiencies in the procoagulant factors VII, X, V, and II and fibrinogen (PT; fig. 1A) or proteins of the contact system, factors XI, IX, VII, X, V, and II and fibrinogen (aPTT; fig. 1A). The decreases in procoagulant proteins, however, are accompanied by decreases in anticoagulant proteins (antithrombin, protein C, protein S). These proteins exert key functions in regulation of coagulation. Importantly, the PT and

aPTT are not influenced by any of the anticoagulant proteins, and these tests therefore do not reflect the balance between pro- and anticoagulants (fig. 1B). These tests are thus unsuitable to assess hemostatic status in a patient with liver disease, although the PT has value as a liver function marker.¹³ One of the reasons the balance between pro- and anticoagulant proteins is difficult to test in a plasma-based coagulation assay is the fact that the protein C pathway (in which protein S is a key cofactor) is initiated by the endothelial cell transmembrane protein thrombomodulin. Specifically, when thrombin binds to thrombomodulin, thrombin transforms from a procoagulant able to form fibrin and activate platelets to an anticoagulant. Thrombin-bound thrombomodulin activates protein C to activated protein C, which dampens coagulation by inactivating procoagulant factors Va and VIIIa (fig. 1B). The key problem in testing this process in the laboratory is the absence of endothelial cells (and hence thrombomodulin) in plasma. Addition of a soluble form of thrombomodulin to test mixtures of advanced coagulation assays, such as thrombin generation tests, has overcome this limitation, but unfortunately such tests are not available for clinical use.

The commensurate decline in pro- and anticoagulant proteins results in a reset of the hemostatic balance that is not detected by coagulation screening tests.¹⁴ However, when the hemostatic balance is tested by assays that do take the balance between pro- and anticoagulant proteins into account (notably by thrombomodulin-modified thrombin generation assays), normo- to even hypercoagulability has been demonstrated by multiple groups.^{5,15–18} Importantly, the hemostatic balance remains intact during major surgery (notably liver transplantation), even

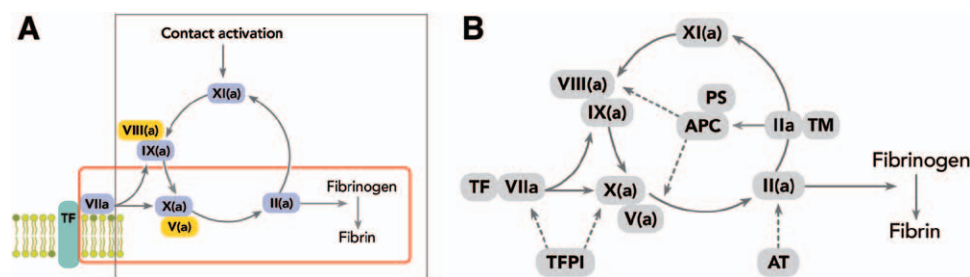


Fig. 1. (A) Schematic representation of the procoagulant part of the coagulation cascade, indicating the proteins for which the prothrombin time (PT; red) and activated partial thromboplastin time (aPTT; gray) are sensitive. The proteins of the contact activation pathway are not depicted for clarity and because these proteins are not required for physiologic hemostasis. (B) Schematic representation of the coagulation system. Exposure of tissue factor (TF), a transmembrane protein present on numerous cell types in the extracellular matrix, initiates the coagulation system via activation of coagulation factors IX and X by the TF-VIIa complex. Thrombin is generated by the intrinsic and extrinsic tenase system (which consists of activated coagulation factors IXa and Xa complexed with their nonenzymatic cofactors VIIIa and Va, respectively). Thrombin-mediated activation of coagulation factor XI further amplifies thrombin generation. Thrombin is a central enzyme in the hemostatic system as it not only converts fibrinogen to fibrin, but it is also an activator of platelets and has multiple other substrates that regulate hemostasis. Thrombin formation is regulated by anticoagulant proteins (interrupted lines) that act in the initiation phase (tissue factor pathway inhibitor [TFPI]), inactivate the nonenzymatic cofactors VIIIa and Va (the protein C system), and directly inactivate thrombin (antithrombin [AT]). The protein C pathway is initiated by the thrombin-thrombomodulin (TM) complex. Once thrombin binds TM, which is a protein localized on endothelial cells, it loses the ability to convert fibrinogen to fibrin and becomes able to activate protein C. Activated protein C (APC) together with its nonenzymatic cofactor protein S (PS) enzymatically inactivates VIIIa and Va.

though substantial further prolongations of the PT and aPTT occur intraoperatively.¹⁹

Hypofibrinogenemia

As fibrinogen is an acute phase protein, levels are relatively well preserved in mild to moderate disease, but levels decrease in more advanced disease. In addition to decreased levels, a functional defect leading to delayed fibrin polymerization has long been recognized.²⁰ Surprisingly, however, it was recently shown that despite decreased plasma fibrinogen levels and delayed fibrin polymerization, the quality of the fibrin clot that is ultimately formed may be relatively normal, and potentially the decreased fibrinogen concentration is balanced by a more thrombogenic nature of the fibrin structure.²¹ Nevertheless, the minimal fibrinogen concentration required for adequate hemostasis in patients with liver diseases has not been established but has been reviewed previously for other surgical patients.²²

Rebalanced Hemostasis in Patients with Liver Disease

Thus, although routine diagnostic tests of hemostasis are frequently abnormal, more advanced laboratory testing suggests the hemostatic status is intact and even has multiple hypercoagulable features.^{14,23} The intact hemostatic balance of patients with liver disease does not appear to be as stable as the hemostatic balance in individuals with a normal liver function, and minor changes can tip the hemostatic balance toward either bleeding or thrombosis (fig. 2). Four lines of clinical evidence support the notion that abnormal hemostasis tests in patients with liver disease do not reflect hemostatic capacity. First, abnormal screening tests do not predict the bleeding risk of a wide range of small and larger invasive procedures,^{6–8} although thrombocytopenia has been suggested to increase bleeding risk in one study. Second, normalization of the PT by recombinant factor VIIa did not reduce blood loss and transfusion requirements during liver transplantation.²⁴ Third, in the past 10 to 15 yr, multiple centers have

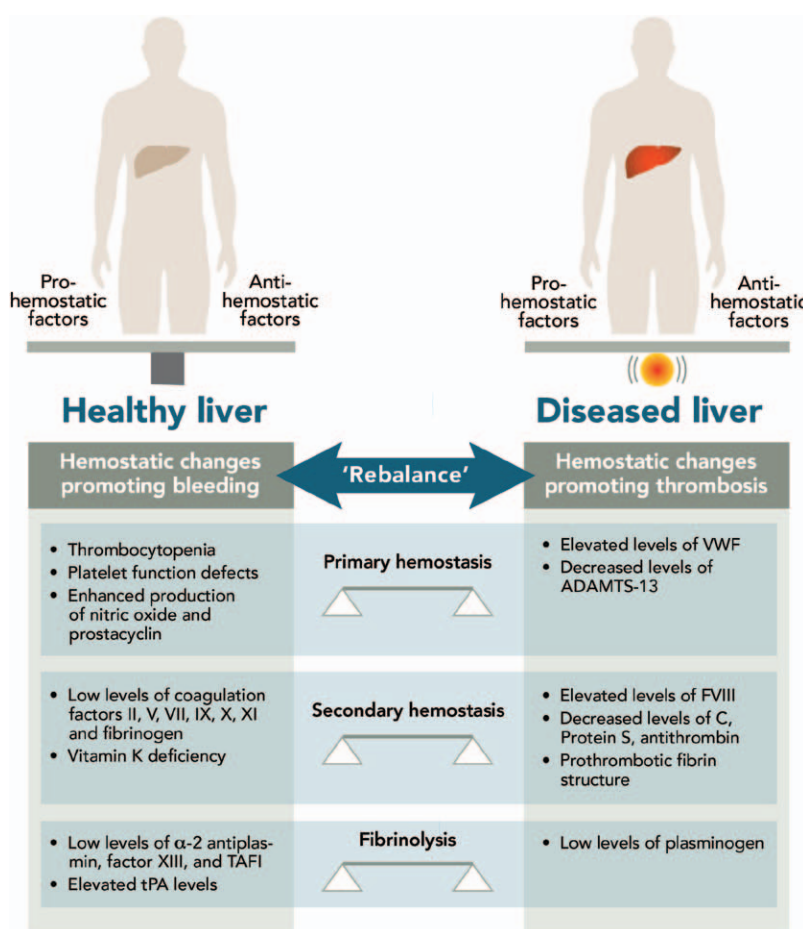


Fig. 2. The hemostatic balance in patients with liver disease as compared to that of healthy individuals. The cartoons depict the stable hemostatic balance in healthy individuals and show that although the hemostatic system in patients with liver disease is (re)balanced, the balance is fragile and may easily tip to either a hypo- or hypercoagulable status (reprinted with permission from Lisman T, Kamphuisen PW, Northup PG, Porte RJ: Established and new-generation antithrombotic drugs in patients with cirrhosis—Possibilities and caveats. *J Hepatol* 2013; 59:358–66). The bottom part of the figure depicts all pro- and antihemostatic changes in patients with liver disease and shows a rebalance of all major components of hemostasis.

demonstrated the feasibility of transfusion-free liver transplantation, even in patients with a substantially prolonged PT at baseline.²⁵ Thus, major and lengthy surgical procedures such as liver transplantation can be performed without any prophylactic or therapeutic administration of fresh frozen plasma (FFP) or platelet concentrate. One center has reported transfusion-free liver transplantation in more than 80% of a consecutive series of 700 patients.⁷ These clinical findings thus provide support for a competent hemostatic balance in patients with (end-stage) liver disease. Fourth, accumulating clinical evidence suggests that patients with liver disease are not protected from thrombotic complications. On the contrary, studies have suggested that liver disease is a risk factor for venous thrombosis, and portal vein thrombosis is common in patients with end-stage liver disease.^{26,27}

Prophylactic Transfusion Based on Preoperative Coagulation Tests in Patients with Liver Diseases Should Generally Be Avoided

There are important limitations of routine diagnostic hemostasis tests in the preoperative setting, as they may not provide accurate information on the hemostatic status, have little relation to bleeding risk, and may not provide clinically relevant information.^{28–31} These limitations hold true for the general population, perhaps with the exception of prediction of bleeding risk in patients on antiplatelet drugs undergoing cardiac surgery³² but are particularly relevant for patients with liver disease as a large proportion of patients with moderate to severe liver disease have profound abnormalities in these test results. A more rational approach includes estimating perioperative bleeding risk with a structured bleeding history,³³ although the predictive value of clinical bleeding scores has, to our knowledge, never been evaluated in patients with liver disease.

Most centers will routinely perform hemostasis testing for ASA III and IV patients, supported by the NICE guidelines. Even though local policies are slowly changing based on the emerging awareness of preserved hemostatic capacity in patients with liver diseases, many centers still prophylactically transfuse platelet concentrates or FFP in patients with liver disease and prolonged coagulation tests who need to undergo invasive procedures. Multiple reasons to avoid prophylactic platelet or FFP transfusion in these patients exist. (1) The efficacy of prophylactic transfusions has never been proven, and emerging evidence suggests platelet and FFP transfusion to be without benefit.^{34–36} In addition, *in vitro* studies have demonstrated that the hemostatic status of patients with liver diseases does not change despite improvement of the platelet count by platelet concentrates³⁷ or improvement of the PT by FFP.³⁸ (2) Large doses of platelets and large volumes of FFP are required to appreciably lower the PT in patients with liver disease. The consequence of infusion of large volumes in patients with portal hypertension and impaired cardiac function is a further increase in

portal and central venous pressure, which promotes bleeding when surgical damage is inflicted. (3) Although blood products are extremely safe in terms of viral transmission, transfusion reactions, albeit rare, may occur. In addition to classical transfusion reactions, more recently recognized complications such as transfusion-related acute lung injury may occur and should be considered when blood products are administered prophylactically. (4) Blood product transfusion during liver transplant surgery has been associated with increased mortality in propensity-adjusted analyses.³⁹ (5) Prophylactic platelet and FFP transfusions are associated with considerable cost.³⁵ However, platelet or FFP prophylaxis may need to be considered for certain procedures such as placement of an intracranial pressure monitor in a patient with acute liver failure. Low-volume prohemostatics such as prothrombin complex concentrates (PCC), fibrinogen concentrate, and recombinant factor VIIa may be valuable alternatives for platelets or FFP in this setting, but clinical experience is limited. A number of small studies have suggested a benefit of recombinant factor VIIa in acute liver failure,^{40,41} but the thrombotic risk is of concern.⁴²

A Wait-and-See Policy or Alternative Measures to Avoid Bleeding?

We have previously argued that during liver transplant surgery a wait-and-see policy is preferred over prophylactic blood component transfusion.³ Preoperative abnormalities in routine hemostasis screens are accepted, and blood components are only transfused when active, nonsurgical bleeding occurs. This wait-and-see policy can likely be safely adopted in many other surgical procedures in patients with cirrhosis.

As an alternative, pharmacologic prohemostatic strategies may be beneficial to reduce the bleeding risk during invasive procedures in patients who are perceived to be at risk for bleeding. PCCs may improve hemostatic status in patients with cirrhosis as evidenced by observational data comparing FFP and PCC-based hemostatic management during liver transplantation.⁴³ However, high-quality data on safety and efficacy of PCCs in patients with liver disease are lacking. We are currently performing a multicenter randomized controlled trial comparing prophylactic PCC with placebo on transfusion requirements and blood loss during liver transplantation.⁴⁴ We are using a four-factor PCC that contains both pro- and anticoagulants (VII, IX, X, II, protein C, protein S, and a small amount of antithrombin), with the aim to stabilize both the pro- and anticoagulant arms of the coagulation system. The advantage of PCCs over FFP is the small volume, and we hypothesize that increasing plasma levels of pro- and anticoagulants without inducing volume overload will improve the hemostatic balance and further reduce perioperative bleeding risk. A secondary endpoint in the trial is the occurrence of thrombotic complications. When the trial would demonstrate that this PCC reduces transfusion requirements and blood loss during liver transplantation, but at the expense of increased thrombotic events, an

alternative strategy combining a PCC with antithrombin concentrate to better stabilize the anticoagulant pathways might be tested in subsequent clinical trials. Fibrinogen concentrates may also improve hemostatic status, either as monotherapy or in combination with PCCs. *In vitro* addition of fibrinogen concentrate was shown to substantially improve fibrin clot quality in samples taken during liver transplantation.⁴⁵ A recent randomized controlled trial showed no reduction in transfusion requirements during transplantation by prophylactic administration of fibrinogen concentrate. A caveat of this trial, however, was that perioperative fibrinogen levels did not substantially differ between the fibrinogen prophylaxis and placebo groups, which partly relate to the fact that the placebo group did receive therapeutic doses of fibrinogen intraoperatively.⁴⁶ Antifibrinolytics have been shown to reduce transfusion requirements during liver transplantation⁴⁷ with a favorable safety profile.⁴⁸ Although hyperfibrinolysis is a distinctive feature of liver transplant surgery, antifibrinolytics also improve hemostasis in patients without overt hyperfibrinolysis (for example, in patients with von Willebrand disease) and may therefore also be useful in patients with cirrhosis undergoing nontransplant surgery. Finally, recombinant factor VIIa likely does not have a role in prevention of bleeding in patients with cirrhosis but may be used as a rescue agent in patients with intractable bleeding.⁴⁹

In aggregate, clinical studies on safety and efficacy of a wait-and-see policy and on prophylactic strategies using PCCs, fibrinogen concentrate, or antifibrinolytics are warranted to define optimal strategies in patients with liver diseases undergoing surgery.

New Developments and Future Directions

Although the concept that the PT does not predict procedural bleeding risk in patients with liver disease is gaining acceptance, clinicians are still interested in a laboratory test that would predict bleeding as, although procedural bleeding risk is much lower than commonly anticipated, clinically relevant bleeding complications do occur. Thrombomodulin-modified thrombin generation testing may accurately assess hemostatic capacity, but the complexity of the test has hampered the development of this test as a routine diagnostic screening test. Other disadvantages of the test are the fact that thrombin generation (and not clot formation) is used as an endpoint in the test and that the test is performed in platelet-poor or platelet-rich plasma. To overcome these drawbacks, a whole-blood thrombin generation test has been developed, which may eventually become suitable as a bedside test.⁵⁰ Nevertheless, adequate thrombin generating capacity does not necessarily translate to hemostatic competence as adequate levels of functional fibrinogen are required for formation of a stable clot.⁴⁵ Whether whole-blood thrombin generation will be able to accurately assess hemostatic status is therefore uncertain.

Thromboelastography tests (thromboelastography and rotational thromboelastometry) are performed in whole blood and do have clot formation as the read-out of the test. However,

conventional viscoelastic tests are not sensitive for the protein C system and fail to accurately test the balance between pro- and anticoagulants. Test results are often normal in patients with chronic and acute liver diseases,⁵¹ which may indicate that thromboelastography better represents hemostatic status in these patients than conventional coagulation tests.

A recent randomized study has compared bleeding and transfusion requirements in patients with cirrhosis undergoing invasive procedures evaluated by standard hemostasis screening tests (platelet count and PT) and thromboelastography.⁵² A substantial and significant reduction in allogeneic blood product transfusion occurred with thromboelastography without differences in bleeding events between the groups. Importantly, the overall bleeding risk in this study was low, and it is questionable whether the prophylactic transfusions that were administered in the thromboelastography group had any clinical benefit. Another study has shown that thromboelastography may be helpful in predicting procedural bleeding risk and suggested that thromboelastography may be used to guide prophylactic preoperative transfusion.⁵³ Although it would be useful to have a reliable hemostatic test to predict bleeding in patients with cirrhosis, prophylactic administration of blood products or pharmacologic agents may still not be indicated given the uncertain risk/benefit ratio. Well-designed randomized controlled studies assessing efficacy and safety of wait-and-see and various prophylactic strategies in (high-risk) surgical patients are required. In addition, studies examining the value of a structured bleeding history before invasive procedures should be performed. Until these studies become available, evidence from liver transplant surgery strongly suggests that a wait-and-see policy is preferred over strategies in which blood product components are transfused based on routine diagnostic tests of hemostasis.

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Competing Interests

The authors declare no competing interests.

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