Transfusion Medicine Reviews 31 (2017) 245–251

Contents lists available at ScienceDirect

Transfusion Medicine Reviews

journal homepage: www.tmreviews.com

Management of Hemostatic Disorders in Patients With Advanced Liver Disease Admitted to an Intensive Care Unit

Ton Lisman [a,*], William Bernal [b]

[a] Surgical Research Laboratory and Section of Hepatobiliary Surgery and Liver Transplantation, Department of Surgery, University of Groningen, University Medical Center Groningen, GZ, the Netherlands

[b] Liver Intensive Therapy Unit, Institute of Liver Studies, Kings College Hospital, London, United Kingdom

ARTICLE INFO

Available online 23 June 2017

Keywords:
Bleeding
Thrombosis
Liver
Cirrhosis
Acute-on-chronic liver failure
Intensive care
Anticoagulants
Fresh frozen plasma
Prothrombin time
Thromboelastography

ABSTRACT

Patients with liver diseases frequently acquire complex changes in their hemostatic system. Traditionally, bleeding complications in patients with liver disease were ascribed to these hemostatic changes, and liver diseases were considered as an acquired bleeding disorder. Nowadays, it is increasingly acknowledged that patients with liver diseases are in "hemostatic rebalance" due to a commensurate decline in pro- and anticoagulant drivers. Indeed, both thrombosis and bleeding may complicate liver disease. Such complications may be particularly worrisome in critically ill patients with liver disease. This review will outline knowns and unknowns in prediction, prevention, and treatment of bleeding and thrombosis in patients with liver disease admitted to an intensive care unit.

Contents

Patients with chronic or acute liver diseases may develop complications requiring admission to an intensive care unit (ICU). Complications necessitating or complicating an ICU admission include bleeding and thrombosis. Gastrointestinal and procedure-associated bleeds, systemic and local venous thrombosis, and clotting of extracorporeal circuits are

* Corresponding author at: Ton Lisman, Surgical Research Laboratory and Section of Hepatobiliary Surgery and Liver Transplantation, Department of Surgery, University of Groningen, University Medical Center Groningen, BA44, Hanzeplein 1, 9713, GZ, The Netherlands.

E-mail addresses: j.a.lisman@umcg.nl (T. Lisman), william.bernal@kcl.ac.uk (W. Bernal).

http://dx.doi.org/10.1016/j.tmrv.2017.06.002
0887-7963/

all frequent complications in patients with liver disease in an ICU setting. Liver diseases are frequently associated with complex changes in the hemostatic system, as the liver is the site of synthesis for many of the proteins involved in hemostasis [1]. However, despite the ubiquity of hemostatic disturbance in the sicker patients with liver disease, there is a lack of high-quality clinical evidence to guide management of the complex hemostatic disorder in these patients. This review will outline the net effects of the complex hemostatic changes in patients with liver diseases and will provide a pragmatic approach to prevention and treatment of bleeding and thrombosis in critically ill patients with liver disease. We will indicate knowledge gaps and suggest a clinical study agenda which we hope will lead to a more evidenced-based approach to hemostatic issues in critically ill patients with liver disease.

Rebalanced Hemostasis in Patients With Liver Disease

Until recently, liver diseases were considered as a clear example of an acquired bleeding disorder. Indeed, among patients with advancing liver disease, abnormalities in routine indices of hemostasis (such as the prothrombin time [PT], platelet count, and plasma levels of individual coagulation factors) are common, as are spontaneous and procedure-related bleeding episodes. However, 2 observations cast doubt on the common dogma of liver disease as a bleeding disorder. First, routine diagnostic laboratory tests such as the or derived international normalized ratio (INR) do not reflect hemostatic status in patients with complex disorders of hemostasis [2,3]. As the PT is only sensitive for a discrete number of procoagulant proteins, it does not capture the complex interplay between pro- and anticoagulants (Fig 1). Thrombomodulin-modified thrombin generation testing, a research tool that has been widely used to assess hemostatic balance in patients with complex hemostatic changes, is better able to capture the balance between pro- and anticoagulant drivers. Multiple independent studies have demonstrated that the functionality of the coagulation system is intact or even hyperactive in patients with liver disease despite prolongations in the PT [4-10]. In addition, it has been well established that the PT is a poor predictor of future bleeding events in these patients [11-14]. Secondly, although bleeding is common in patients with liver disease, the most frequent major bleeding complication, that is, variceal bleeding, is seldom a consequence of hemostatic failure but is rather a consequence of portal hypertension and local vascular abnormalities [15]. In support of this, anticoagulant therapy does not appear to aggravate the severity of variceal bleeding [16], and procoagulant therapy with recombinant factor VIIa had no effect on severity and outcome of variceal bleeding [17].

In addition to the observations of normal to increased thrombin generation by thrombomodulin-modified thrombin generation tests, it has been shown that other components of the hemostatic system also have intact function despite changes in individual components that in isolation may promote bleeding. Specifically, thrombocytopenia appears to be balanced by a substantial increase in plasma levels of the platelet-adhesive protein von Willebrand factor [18,19], defects in antifibrinolytic proteins are balanced by decreased levels of plasminogen [20], and decreased fibrinogen levels are balanced (in part) by prothrombotic changes in the structure of the fibrin clot [21].

The clinical observations on the apparent lack of a high risk of hemostasis-related bleeding with laboratory evidence of compensatory factors for decreased activities in prohemostatic drivers has led to the concept of "rebalanced hemostasis" [22-24]. Both in patients with cirrhosis and in patients with acute liver failure, the parallel decline in pro- and antihemostatic drivers results in a net hemostatic balance. This new hemostatic balance, however, is thought to be much less stable as compared with that in patients with intact liver function. The hemostatic balance can be offset by yet incompletely understood mechanisms and result in bleeding or thrombosis. As mentioned previously, many (spontaneous) bleeding episodes may be unrelated to hemostatic failure, but hemostasis-related bleeding complications such as bruising, epistaxis, and gum bleeds can be frequent, suggesting that the hemostatic rebalance can easily be disturbed. Conversely, patients with liver disease also experience thrombotic complications. Cirrhosis is a risk factor for deep vein thrombosis and pulmonary embolism [25], and portal vein thrombosis is not uncommon in patients with end-stage disease [26].

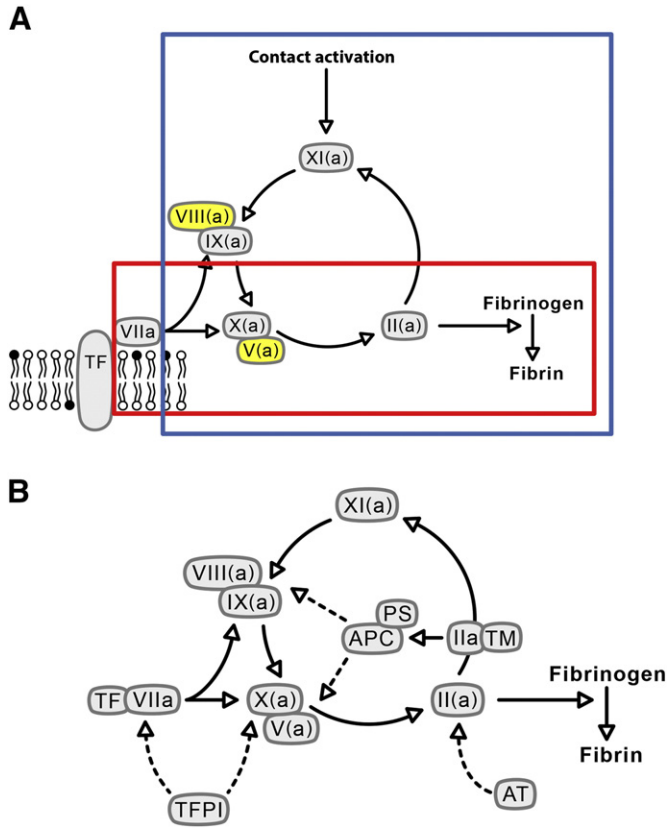

Fig 1. A, Schematic representation of the procoagulant part of the coagulation cascade, indicating the proteins for which the PT (initiated by tissue factor [TF]; red) and APTT (initiated through the contact activation system; blue) are sensitive. The nonenzymatic cofactors VIII and V are indicated in yellow; the enzymatic coagulation factors, in gray. B, Schematic representation of the coagulation system with the 3 natural anticoagulant systems indicated by the interrupted lines. Thrombin formation is regulated by anticoagulant proteins 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.

Clinical Consequences of "Rebalanced Hemostasis"

It is common practice to try to correct laboratory abnormalities of hemostasis in patients with liver diseases prior to invasive procedures by infusion of fresh frozen plasma (FFP) and/or platelet concentrates. However, because the PT/INR does not and the platelet count only marginally predicts procedural bleeding risk [13,14], and as the hemostatic balance in patients with liver diseases appears preserved, this approach has little evidence base. In addition, although many clinicians still anticipate that patients with liver disease will have a substantially increased procedural bleeding risk, this assumption is not supported by data. Commonly performed procedures such as liver biopsy [27], paracentesis [28], and dental work [29] have a low bleeding risk, and those bleeding complications that do occur are not necessarily related to hemostatic failure but may be a consequence of other physical issues including vessel rupture or poor local tissue quality (as for example in dental work). Importantly,