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BRIEF REVIEW

Hepatology

Hemostatic System in Chronic Viral Hepatitis

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Abstract

Hemostasis is balanced by pro- and anticoagulant and pro- and antifibrinolytic factors, most of these being synthesized by the liver. Advanced liver disease is associated with perturbations in the level of these factors due to secretory deficiencies. Thrombocytopenia, reduced levels of factor II-VII-X, and anti-fibrinolytic factors are all features of CHC infection, suggesting hypocoagulability. However, higher concentrations of VWF and factor VIII, as well as lower concentrations of anticoagulant factors including protein C and S, have also been reported in CHC infections, suggesting hypercoagulability. Thus, the hemostatic balance in the patient with liver disease is relatively unstable as evidenced by the occurrence of both bleeding and thrombotic complications in a significant proportion of patients with chronic viral hepatitis.

In patients with chronic liver disease (CLD), in whom extremely complex alterations of hemostasis occur, one cannot rely on levels of individual coagulation factors, or on simplified tests of hemostasis such as the PT or APTT to predict the hemostatic status. To determine the hemostatic status in these patients, more complex tests and a more comprehensive overview of the hemostatic changes are required. In connection with the latest studies, a revision of the methods for correction of hemostatic system disorders in patients with acute and chronic liver diseases becomes urgent.**(International Journal of Biomedicine. 2018;8(2):102-107.)**

Key Words: hemostasis • chronic viral hepatitis • liver diseases • thrombocytopenia • thrombosis • bleeding • coagulopathy

Abbreviations

APTT, activated partial thromboplastin time; **CLD**, chronic liver disease; **CVH**, chronic viral hepatitis; **CHB**, chronic hepatitis B; **CHC**, chronic hepatitis C; **FFP**, fresh-frozen plasma; **HBV**, hepatitis B virus; **HCV**, hepatitis C virus; **HEV**, hepatitis E virus; **PT**, prothrombin time; **TT**, thrombin time; **VTE**, venous thromboembolism; **VWF**, von Willebrand factor.

Introduction

The hemostatic system is based on a delicate equilibrium in which complex interactions between plasma coagulation proteins, cellular elements and the vessel wall occur in order to protect against hemorrhage.[1] The liver plays a central role in the hemostatic system as the majority of coagulation factors and proteins involved in fibrinolysis are synthesized by hepatic parenchymal cells. Furthermore, the liver produces thrombopoietin, which is responsible for platelet production from megakaryocytes.[2] In patients with hepatic parenchymal disease, the loss of functional parenchyma results in decreased synthesis of both coagulation factors and natural anticoagulant proteins.[3-6] In addition, decreased hepatic synthesis of thrombopoietin contributes to thrombocytopenia; systemic intravascular coagulation results in consumption of platelets and hemostatic factors.[7,8] Moreover, splenomegaly in portal hypertension results in increased platelet sequestration in the spleen. In patients with liver disease, systemic activation of endothelial cells results in increased release or production of hemostatic factors.[9,10]

Finally, it should be noted that the hemostatic balance in the patient with liver disease is relatively unstable as evidenced by the occurrence of both bleeding and thrombotic complications in a significant proportion of patients.[2]

In connection with the latest studies, a revision of the methods for correction of hemostatic system disorders in patients with acute and chronic liver diseases becomes urgent.

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The state of the hemostatic system in CLD

In CLD (chronic viral hepatitis, cirrhosis), both pro- and anticoagulant deficiency are observed. In contrast to acute liver disease, this is caused, to a greater extent, by a disorder in the synthesis of proteins of the coagulation and anticoagulation systems in the liver rather than by consumption coagulopathy. Just as with acute liver disease, there is a compensatory increase in VWF and factor VIII, but thrombocytopenia is a hallmark of CLD.

Bulygin and co-authors concluded that in the third stage of CHB, intracellular processes in liver tissue are inhibited, compared to stage 2, with more inhibition of processes associated with synthetic reactions.[11]

As Witkop and colleagues emphasize, in the past, cirrhosis and its complications have caused the majority of the mortality and morbidity of hemophiliacs. Recent advances in the treatment of hepatitis C should substantially decrease the risk of CLD due to HCV infection in hemophilia patients.[12]

In severe forms of cirrhosis, Soria et al.[13] found that fibrinogen levels tend to decrease and abnormal fibrinogen molecules can be detected. Fulminant hepatic failure caused by HEV is accompanied by disseminated intravascular coagulation. However, the pathogenesis of coagulation disorders is poorly understood in hepatitis. In the studies by Geng et al.[14] and Ratra et al.[15], it was found that the HEV ORF3 protein downregulates the expression of FGB (β chain of fibrinogen). Therefore, Geng and co-authors proposed that the decrease in the expression of FGB effected by the HEV ORF3 protein may result in a low concentration of fibrinogen in the blood, thus leading to the pathological disorder of hemostasis. Shao and colleagues found the association between low plasma fibrinogen and poor prognosis in acute-on-chronic liver failure patients.[16] The study by S.Kim and colleagues found that soluble fibrin complex (sFC)—fibrin-related marker—is a powerful diagnostic and prognostic marker of disseminated intravascular coagulation in patient with liver cirrhosis.[17]

Yao and Lv studied the effects of various pre-analytical variables on the values of APTT, D-dimers, fibrinogen, PT and TT in patients with hepatitis B. All tested pre-analytical variables had a moderate effect on the D-dimer, fibrinogen, PT and TT values. Storage for 24h had a large effect on APTT. The results of this study showed that specimens for D-dimer, fibrinogen, PT and TT tests could be stored for 24h, and specimens for APTT could be stored for 8h.[18]

The balance between the procoagulants and anticoagulants is usually investigated by means of laboratory tests, such as the PT and APTT, that are responsive only to procoagulant factors. Because these tests are performed without added thrombomodulin, they are inadequate to explore the physiological mechanisms regulating thrombin formation because they do not allow full activation of protein C.[19] Tripodi and co-authors,[19] using the tests based on the continuous registration of thrombin generation under in vitro conditions that mimic more closely what occurs in vivo,[20] found that the reduction of procoagulant factors in patients with cirrhosis is compensated by the reduction of anticoagulant factors, thus leaving the coagulation balance unaltered. These findings suggest that conventional coagulation tests are unlikely to reflect the coagulation status of these patients.[19] Thus, PT cannot be a reliable indicator of blood coagulation, a predictor for bleeding, or an indication for transfusion therapy. The thrombin generation test is a more reliable indicator for making decisions about infusion of FFP or hemostatic agents, both for normalizing PT and for stopping bleeding.

As mentioned previously, CLD can cause an imbalance in the coagulation system, and a number of single-center and population-based studies have shown that the coagulopathy induced by liver disease may be associated with thrombosis. The incidence and prevalence of VTE among patients with CLD have been estimated in several studies.[21] Evidence suggests that coagulation may influence the development of liver fibrosis in CVH.[22-24] In vitro studies using selective PAR-1 agonists and thrombin demonstrate that these produce rapid stellate cell activation, secretion of extracellular matrix proteins, tissue remodeling and fibrogenesis.[25,26] Thus, hypercoagulability characterized by an increase of thrombin generation within the circulation may contribute to fibrogenesis by enhancing direct activation of stellate cells.

Thus, the traditional coagulation tests, such as PT and APTT, are not suitable to assess the coagulation balance. These tests are indeed poor predictors of bleeding in these patients.[28] Furthermore, the value of infusion of plasma or other procoagulant agents, which is still common practice to stop or prevent bleeding in this setting, is questionable. This is in line with the evidence stemming from recent randomized trials showing that recombinant activated factor VII fails to stop bleeding in patients with variceal hemorrhage[29,30] or during hepatectomy.[31,32]

Anticoagulation may in the future become a therapeutic option for the prevention of liver fibrosis in cases such as recurrent HCV infection after liver transplantation. In the study by Widén, anticoagulation did not increase the risk of bleeding complications after liver transplantation.[33] A UK-based multi-centre phase II study evaluating the anti-fibrotic effect of warfarin anticoagulation therapy in patients transplanted for HCV cirrhosis recently reported interim results, which potentially support these findings. A reduction in fibrosis scores at one year post-OLT in patients treated with warfarin was demonstrated, compared to patients not taking anticoagulation; completion of this study is awaited to validate these findings.[34] Finally, no increased risk of bleeding was reported in an abstract of preliminary results of this study.

Studies of VTE prophylaxis in cirrhotic patients have demonstrated no significant increase in the risk of bleeding with anticoagulation.[35-37] LMWH administered for 1 year subcutaneously at prophylactic dosage prevented the development of portal-vein thrombosis as well as the occurrence of disease decompensation in a randomised controlled study without significant association with bleeding.[38]

CLD patients are variably thrombocytopenic and possibly thrombocytopathic. Numerous studies have addressed the issue of thrombocytopathy in cirrhosis. The role of thrombocytopenia that might explain, at least in part, the bleeding tendency observed in cirrhosis, has been recently attenuated. In vitro experiments in which platelet

adhesion to thrombogenic surfaces was studied using flowing blood have demonstrated that platelet adhesion under the thrombocytopenic conditions of cirrhosis is indeed stimulated by the high levels of VWF present in cirrhotic plasma.[9] The study by Choe and co-authors showed that thrombocytopenic patients with viral infection had a higher frequency of platelet clumping than those with other diseases, which was statistically significant (13.8% vs. 6.5%, respectively: P=0.003). Among the 18 cases where pseudothrombocytopenia (PTCP) or platelet clumping was related to viral infection, hepatitis A virus infection (72.2%) was most common. A failure to recognize PTCP may lead to unnecessary diagnostic tests and patient mismanagement.[39] Sitia and colleagues[40] suggested that platelets may be key players in the pathogenesis of HBV-associated liver cancer and support the notion that immune-mediated necroinflammatory reactions are an important cause of hepatocellular transformation during CVH. On the contrary, Alkozai and colleagues[41] found no evidence of basal platelet activation in patients with cirrhosis compared to controls. The authors argue that HCC development or recurrence in patients with hepatitis B- or C-related cirrhosis does not appear to be associated with platelet activation and changes in pivotal proteins in primary hemostasis.

The study by Tripodi and colleagues[42] showed that severe thrombocytopenia might limit thrombin generation in patients with cirrhosis. These findings —together with the observation that thrombin generation is normal in the plasma of individuals with cirrhosis[19]—might justify platelet transfusion or treatment with recombinant human thrombopoietin[43] in those patients with severe trombocytopenia when they bleed spontaneously or before undergoing surgery or liver biopsy.

A phase 2 study showed that eltrombopag— an oral thrombopoietin-receptor agonist approved for use in patients with chronic immune thrombocytopenia—could increase platelet counts in patients with thrombocytopenia and hepatitis C.[44] In the study by Afdhal and co-authors,[45] eltrombopag reduced the need for platelet transfusions in patients with chronic liver disease who were undergoing elective invasive procedures, but it was associated with an increased incidence of portal-vein thrombosis, as compared with placebo.

Thus, in any situation where platelet transfusion is being considered, all risks must be balanced against the potential clinical benefits.

The liver is the main site of the synthesis and/or clearance of the proteins involved in fibrinolysis. Therefore, CLD, including cirrhosis, leads to altered plasma levels of fibrinolytic proteins. Hyperfibrinolysis is thought to contribute to bleeding associated with advanced cirrhosis. Recent work has suggested that thrombin-activated fibrinolysis inhibitor (TAFI) is decreased in liver cirrhosis.[46] However, decrease in TAFI is counterbalanced by the concomitant decrease in profibrinolytic factors, and excessive fibrinolysis does not occur in patients with liver disease. Nevertheless, it is now recognized that hyperfibrinolysis may occur in 30 to 50% of patients with end-stage liver disease. A causal role of hyperfibrinolysis in bleeding is also difficult to establish because of other concomitant changes in hemostasis that occur.[47]

Thus, numerous studies have reported reduced synthesis of various hemostatic factors in CLD patients. Whether changes in plasma levels of these proteins reflect recovered liver synthetic function following virological eradication therapy has not been approved yet. The aim of the study by Saray et al.[48] was to determine the impact of sustained viral suppression achieved with pegylated interferon alpha and ribavirin on hemostatic parameters including natural anticoagulants in patients with chronic hepatitis C. Authors found that protein C and protein S are sensitive markers of hepatocyte synthetic impairment and are valuable markers in monitoring the efficacy of antiviral treatment in CHC patients.

In the treatment of liver diseases and their complications, antiviral drugs, geratoprotectors, antibiotics and other medications are used, and some of them can affect the hemostatic system. The current standard treatment for CHC infection is pegylated interferon (PegIFN)-α plus ribavirin treatment for 48 weeks' duration for patients with HCV genotype 1 or 4 (HCV-1/4), and for 24 weeks' duration for patients with HCV genotype 2 or 3 (HCV-2/3).[49] Two preparations of PEG-IFN are currently available: Peg-IFN alfa-2a (40 kD; fixed dose) and PEG-IFN alfa-2b (12 kD; weight based). Several large randomized-clinical trials have now demonstrated that a majority of patients can achieve a sustained virological response (SVR) with these regimens.[50-52] Unfortunately, adverse effects related to IFN or RBV are relatively common and may lead, especially after the first 24 weeks of treatment, to dose reduction or discontinuation of treatment. The most frequent adverse effects include flu-like symptoms, myalgia, fatigue, gastrointestinal disturbances, psychiatric disorders and hematological abnormalities (anemia, neutropenia, thrombocytopenia).[53] The primary toxicity of ribavirin is hemolytic anemia, which was observed in approximately 13% of all COPEGUS/PEGASYS-treated subjects in clinical trials. COPEGUS/PEGASYS therapy should be discontinued in hemoglobin <8.5g/dL in patients with no cardiac disease, or hemoglobin <12g/dL despite 4 weeks at reduced dose in patients with a history of stable cardiac disease.[54]

The peculiarity of the change in the hemogram in interferon therapy is the long-term recovery of normal parameters; thus, in 6 months after the cessation of treatment the number of platelets and leukocytes may be at the subnormal level.

To correct the coagulation disorders in patients with chronic and acute viral hepatitis, etamsylate is used, which has hemostatic, angioprotective and proaggregant effects. It stimulates the formation of platelets and their exit from the bone marrow, activates the formation of tissue thromboplastin at the site of damage to small vessels, promotes adhesion and aggregation of platelets, reduces bleeding, and restores the pathologically altered bleeding time. Etamsylate does not affect the normal parameters of the hemostatic system. Viekira Pak (ombitasvir/paritaprevir/ritonavir & dasabuvir), daclatasvir, tenofovir, and myrcludex B are all undergoing clinical trials. Hepatoprotectors (silymarin, heptral, inosine, etc.) also have no adverse effects on the coagulation system.

Antiviral medications in the treatment of CHB (lamivudine, adefovir, telbivudine) are not accompanied

by significant changes in the peripheral blood. At the same time, Iannacone and colleagues[55] have identified platelets as important agents in the pathogenesis of HBV-related liver disease by sustaining the intrahepatic accumulation of virus-specific T cells, the intrahepatic expression of pro-inflammatory cytokines, and chemotactic factors that promote the recruitment of antigen, nonspecific inflammatory cells. They found that two platelet-specific activation inhibitors, aspirin, which blocks thromboxane A2 production, and clopidogrel, which blocks the P2Y12 ADP receptor,[56] reduced the accumulation of virus-specific CD8+ T cells in the liver and the associated liver damage when administered alone or as a combination therapy. The combined use of aspirin and clopidogrel ameliorates the course of immune-mediated chronic hepatitis and HCC progression through distinct pharmacological effects. The synergistic action of these two drugs may represent a new therapeutic strategy to reduce the platelet-dependent accumulation of pathogenic virus-specific CD8+ T cells, and consequently, the accumulation of virus-nonspecific inflammatory cells, hepatocellular injury and compensatory proliferation, liver fibrosis and HCC development.[57] The long-term daily administration of anti-platelet therapy in patients who are at a low risk of bleeding during the early stages of chronic disease may be beneficial in reducing thrombosis, which is often observed in selected groups of patients with pro-coagulant imbalance.[21]

As noted earlier, two randomized controlled studies have evaluated the effect of recombinant factor VIIa (rFVIIa) on variceal bleeding in cirrhosis or during hepatectomy without showing significant benefit.[30,31]

The efficacy of FFP and platelet concentrate infusion to avoid bleeding also has never been demonstrated.[58] Moreover, complete normalization of laboratory parameters in cirrhotic patients is rarely achieved by administration of platelet concentrates or FFP.[59,60] It should be noted that arbitrary PT cut-off values are still used as a yardstick to guide treatment with FFP or other pro-coagulant agents in patients undergoing invasive procedures. Tripodi and colleagues[61] showed that thrombin generation in patients with cirrhosis does not appreciably change after in vitro addition of pooled normal plasma even though PT and APTT shortening would suggest otherwise. These results question the validity of the PT as a stand-alone test to guide transfusion of FFP in the setting of CLD. Broader implementation of a restrictive transfusion policy in patients with liver disease may have a profound impact in blood product use, and may even result in reduced morbidity and mortality.[2]

Conclusion

Thus, there has been tremendous progress in understanding the hemostatic abnormalities in patients with liver disease. The longstanding dogma that patients with liver disease have a hemostasis-related bleeding tendency is no longer supported by data from both clinical and laboratory studies.[2] In patients with liver disease, there are extremely complex alterations of hemostasis with a high risk for both bleeding and thrombosis. However, these complications are not reflected in routine tests of hemostasis. Rebalanced hemostasis in CLD requires additional studies to define optimal diagnostic and treatment strategies to prevent or treat bleeding and thrombosis in patients with liver disease.

Conflict of interest

The authors declare that they have no conflicts of interest to disclose.

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