ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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The Coagulation Disorders of Severe Liver Disease

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H&O What is the role of the liver in coagulation?

AS The liver is very important for coagulation; it regulates portal pressure and influences the reservoir of platelets. Protein synthesis and the action of platelets are influenced by the liver. Indigenous anticoagulant factors also play a significant role.

H&O What is the pathogenesis of severe liver disease?

AS The main pathogenesis of severe liver disease is related to hepatic blood flow reduction, which simultaneously produces an increase in the portal vein pressure. These events have a clear influence in the chain of coagulation impairment produced as the disease advances.

H&O How is coagulation affected in patients with severe liver disease?

AS Advanced cirrhotic disease produces a complex balance between procoagulant and antihemostatic actions[1-3] characterized by a decreased level of hemostatic proteins; low synthesis of anticoagulants (ATIII, protein C); thrombocytopenia; an increase of von Willebrand factor, human factor VIII, nitric oxide, and prostacyclin; and a subtle equilibrium between tissue plasminogen activator (tPA) and plasminogen activator inhibitor-1. Consequently, thrombin generation is maintained. Therefore, an increase of thrombogenicity related to the predominance of procoagulant factors, especially in nonalcoholic cirrhotic disease, may be found.

H&O How common are coagulation disorders in patients with severe liver disease?

AS In patients with liver disease, plasma levels of thrombin-activated fibrinolysis inhibitors—as well as other fibrinolytic inhibitors, such as antiplasmin—are profoundly reduced. In spite of this, the plasma fibrinolytic potential in patients with stable cirrhosis is similar to that of healthy controls. In some cases where there is infection, sepsis, or hypotension, a depletion of anticoagulant factors—such as protein C or antithrombin 3—is produced. These patients usually have experienced an injury, had an abdominal infection, or underwent a major surgical procedure. Thrombocytopenia, which is very common, is related to portal hypertension. Further deterioration occurs in these patients and is characterized by a global reduction of all coagulation factors; a decrease in antithrombotic factors (antithrombin III, protein C), plasminogen activator inhibitor factors, and other natural antifibrinolytic agents (alpha 2-antiplasmin); and the simultaneous generation of tPA.[4]

H&O How are coagulation disorders diagnosed in these patients?

AS There is limited correlation between conventional hemostasis and coagulation tests and increased bleeding during liver surgery, including liver transplantation. Such tests therefore cannot be used to predict which patients will require more blood products during surgery. Assessment of hemostasis and coagulation requires the careful

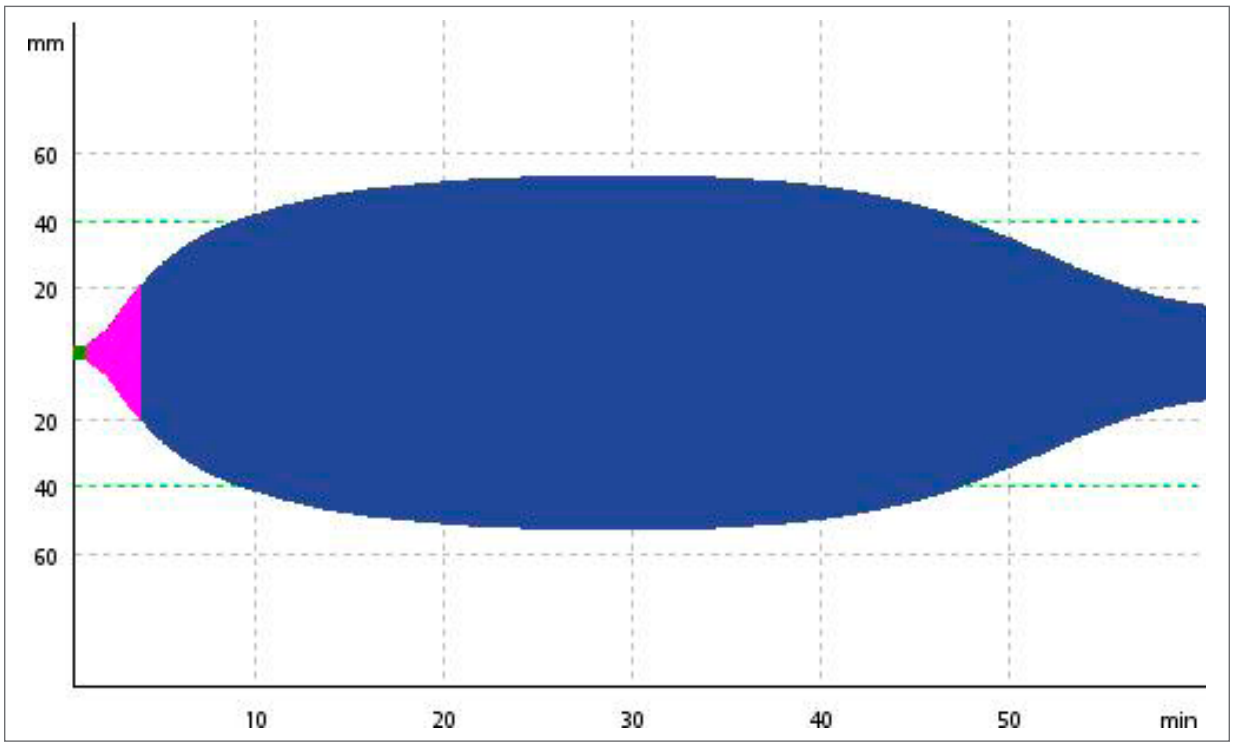

Figure 1. Image from rotational thromboelastometry performed during a liver transplantation. Moderate alteration of coagulation with signs of severe fibrinolysis at reperfusion of the liver graft is demonstrated. The green area at left indicates the clotting time, which is influenced by the level of plasmatic coagulation protein factors. The pink area indicates the clot formation time, which is influenced by clot polymerization. The blue area indicates clot firmness, which is influenced by clot substrates, mainly fibrinogen and platelets. Clot firmness may be measured 10 minutes after the clot formation time, which significantly correlates with the maximum clot firmness. The decrease of clot firmness is a measure of fibrinolysis, and indexes are determined at 30 and 60 minutes after the clot formation time.

evaluation of individual patients ("point of care monitorization"). Thromboelastography (TEG) has been used in the operative management of liver transplant patients (Figure 1). In the cirrhotic patient, the TEG pattern is characterized by a decrease in maximum clot firmness and clot formation time, with a good correlation with fibrinogen, antithrombin III, and platelets.[5] During liver transplantation, the profile of coagulation is characterized by thrombocytopenia and hypofibrinogenemia, with a good correlation with maximum clot firmness at 10 minutes during TEG.[6,7]

H&O What are the morbidity and mortality associated with coagulation disorders in severe liver disease?

AS Bleeding during liver transplantation or other major interventional procedures may occur as a result of decreased clotting factors caused by surgical bleeding, facilitated by an increase of the portal hypertension and the oesophagus-gastric venous distension caused by compressive maneuvers and vascular clamping. Corrections of hematologic disturbances by the administration of crystalloids, platelets, and clotting factors can be affected by acidosis, hypocalcemia, and hypothermia. In addition, fibrinolytic enzymes released from damaged cells can lead to increased fibrinolysis of blood clots already formed. This reinforces the importance of the transluminal flow in portal vessels. Preservation of the vena cava during liver transplantation helps to reduce bleeding. At the time of the graft reperfusion—depending on the graft quality—further deterioration can occur, characterized by a global reduction of all coagulation factors, a decrease in antithrombotic factors (antithrombin III, protein C), a decrease in plasminogen activator inhibitor factors and other natural antifibrinolytic agents (alpha 2-antiplasmin), and the simultaneous generation of tPA.[4] Also, formation of D-dimer complexes occurs, in particular, at the end of transplantation or in the immediate postoperative period. Bleeding during the intraoperative and immediate postoperative period is one of the most common causes of death. Patients who receive massive transfusions have a high mortality rate and a higher incidence

of infection, which increases with the number of red blood cell units administered. The connection between transfusion and infection has been confirmed in different surgical situations and acute surgical trauma patients.[8] There is also a positive correlation between the incidence of multiple organ failure and the number of red blood cell units used, suggesting that adverse effects can be associated with immunomodulatory allogeneic blood transfusions.[9] In our experience with liver transplantation, requirements of blood products were the main determinant of operative mortality and the occurrence of postoperative renal dysfunction.[10-12]

H&O What factors contribute to the use of preventive therapy, and what does such therapy consist of?

AS Preventive therapy will vary according to the type of patient. For patients with thrombotic tendencies, we use oral anticoagulant drugs. In patients who mainly have bleeding disorders, we try to reduce the portal hypertension with beta-blockers and other vasopressors. In these cases, we try not to use fresh frozen plasma or other procoagulant factors.

H&O When is rescue therapy required, and what does it consist of?

AS Rescue therapy is more important when there is active bleeding. In this case, we favor the fibrinogen and platelet reposition guided by TEG data. Because anemia influences the blood product requirement, it would be interesting to explore the benefits of iron administration.

H&O Are there any areas of ongoing research?

AS Although implementation of corrective strategies based on the administration of prothrombotic factors and antifibrinolytic drugs are common during liver transplantation, concern about unwanted thrombotic events is a major limitation of preventive therapy even when used to correct mild alterations of hemostasis and coagulation. Criteria for identifying those patients who could benefit from preventive treatment because of higher risk of bleeding, or, on the contrary, those patients who are at risk of perioperative thrombotic events, have not been elucidated. Endogenous hemostatic expression at different stages of liver transplantation can be investigated through analysis of anticoagulation biomarkers (thrombomodulin, protein C, antithrombin), fibrinolysis biomarkers (plasminogen activator inhibitor, tissue plasminogen activator, plasminogen-alpha 2–antiplasmin complexes, D-dimers), and thrombotic biomarkers (thrombin-antithrombin complexes, factor II fragments, factor VIII, and thrombin generation expressed as a G-index on TEG).

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