Management of coagulopathy in patients with liver disease undergoing surgical intervention

Atul B Mehta

Department of Hematology, Royal Free and University College School of Medicine, London

Patients with liver disease are at substantially increased risk of both thrombosis and hemorrhage. Careful clinical and laboratory assessment is crucial and the need for better assessment tools (particularly suitable for use at the bedside) is recognized. Blood component therapy and vitamin K are of established value. The availability of new drugs, particularly aprotinin and recombinant factor VIIa, has substantially helped the outlook for patients with liver disease undergoing elective and emergency surgical intervention. [Indian J Gastroenterol 2006;25(Suppl 1):S19-S21]

The liver is the cornerstone of the coagulation system (Table 1). The consequences of liver disease (Table 2) include consumption of clotting factors and platelets (due to endothelial cell damage, disseminated intravascular coagulation [DIC], tissue necrosis, increased fibrin breakdown, hypersplenism) as well as failure to synthesis procoagulant and anticoagulant proteins. Bleeding and thrombosis are important manifestations, particularly in patients who are challenged by infection or surgery.

Laboratory tests used for assessing the severity and indicating the underlying mechanism of the coagulopathy include the following: platelet count, fibrinogen level, prothrombin time, APTT, thrombin time, and fibrin degradation products/D-dimer assays. Other tests that are helpful include the IVY template bleeding time, and specific factor levels (factor V, factor VII, factor VIII, antithrombin, and factor Xa). Deficient production of the coagulation factors II, VII, IX and X (all vitamin K dependent) will lead to a disturbance of coagulation revealed by a prolonged prothrombin time. Patients with severe deficiencies may also exhibit a prolonged activated partial thromboplastin (APTT).

Table 1: Role of liver in coagulation
- Synthesis of coagulation factors
- Absorption of vitamin K (II, VII, IX, X)
- Clearance of activated coagulation factors FDPs
- Plasminogen activations
- Control of coagulation and thrombosis
  - Anti-thrombins
  - Proteins C and S via vitamin K

Table 2: Consequences of liver disease for coagulation
- Predisposition to disseminated intravascular coagulation
- Accelerated or decreased fibrinolysis
- Thrombocytopenia
- Qualitative defects, e.g., in platelet function dysfibrinogenemia
- Fluid overload, dilutional anemia
- Increased susceptibility to infection

Mild liver disease is associated with cholestasis and vitamin K deficiency; however, in advanced liver failure this abnormality may not be correctable even with oral or parenteral vitamin K. Thrombocytopenia occurs for a range of reasons in patients with liver disease. The liver is the primary site of synthesis of thrombopoietin, which is the primary stimulus to the bone marrow for platelet production. Enlargement of the spleen caused by portal hypertension leads to destruction and trapping of platelets within the spleen. Patients with advanced liver disease also demonstrate increased fibrinolytic activity, they have a predisposition to DIC, and they are susceptible to infection.

Infection as a cause of coagulation disturbance

Reduced reticuloendothelial activity, neutrophil dysfuncion, splenic hypofunction, complement abnormalities and other mechanisms all contribute to the increased susceptibility to infection of patients with liver disease. A recent study using thromboelastography found increased ‘heparin’ activity in blood of patients with cirrhosis and bacterial infection, but not in non-infected patients; this effect disappeared after resolution of infection. Patients with cirrhosis have increased anti-factor Xa activity, an increased level of heparin sulphate released by the action of endotoxin on endothelium, and the increase in mast cells seen in these patients leads to an increase in tissue plasminogen activator levels. This increases susceptibility to DIC, and directly leads to deficiencies in the protein C system.

Why are patients with liver disease more susceptible to DIC?

It is now clear that DIC involves activation of the extrinsic coagulation pathway, which is critically...
dependent on tissue factor and factor V. Tissue damage, particularly damage to the endothelium, triggers the following:

1. Inflammation and increased levels of a range of cytokines. This activates mononuclear cells and increases the expression of tissue factor and factor 7a on the surface of these cells, which triggers the coagulation pathway.

2. Endothelial damage causes significant embarrassment to physiological anticoagulant mechanisms. Protein C levels are reduced, thrombomodulin is reduced, and both of these lead to increased fibrin formation. Plasminogen activator inhibitor (PAI-1) is increased and this leads to deficient removal of fibrin.

3. Anticoagulant systems are depressed. Anti-thrombin levels are reduced (particularly affecting factors Xa and IIa). Protein C levels are reduced (particularly affecting factors VII, IXa and Xa) and protein S levels are reduced as elevated acute-phase proteins (including complement C4) increase binding of free protein S.

**How is severity of DIC measured?**

A recent DIC scoring system measures the severity in patients who have a definable cause / underlying predisposition. Key coagulation parameters (Table 3) must be measured and the score is based on thrombocytopenia, levels of fibrin-related markers, thrombin time, and fibrinogen level. Serial measurement of the score helps the assessment of patients with acute bleeding.

**Management**

**Emergency**

Adequate laboratory assessment (Table 3) must be undertaken immediately. The use of red blood cell transfusions to compensate for hemorrhage is crucial. Fresh frozen plasma should be used to replace coagulation factors and the numbers of units transfused can be regulated by regular measurement of the APTT and other coagulation parameters. Patients with fluid overload will benefit from the use of cryoprecipitate. Platelet transfusion should be used to elevate the platelet count to greater than 50 x 10^9.

**Table 3: Tests prior to surgical intervention in liver disease**

- Full blood count, platelets
- PT, APTT, thrombin time, fibrinogen level
- Fibrin degradation products
- Thromboelastography
- Blood group, antibody screen

**Table 4: Therapeutic agents for controlling bleeding in patients with liver disease undergoing surgery**

- Blood components
  - Red cells
  - Fresh frozen plasma
  - Cryoprecipitate
- Vitamin K
- Tranexamic Acid
- Erythropoietin
- Recombinant factor VII
- Aprotinin
- Cell salvage (autotransfusion)

L. Thromboelastography can be useful in assessing the need for blood component replacement and the ongoing efficacy of such replacement therapy. Hematologists increasingly recognize that *in vitro* laboratory tests are of limited usefulness and bedside tests such as thromboelastography and clinical assessment are crucial to successful management.

Management strategies are indicated in Table 4. Tranexamic acid can be critically useful in limiting fibrinolysis. Aprotinin is helpful. Recombinant factor VIIa has made a major impact on the management of patients with severe bleeding both in the emergency setting and also the elective setting. A recent review has identified 37 articles on the use of recombinant factor VIIa, which record experience in nearly 700 patients. Factor VIIa will clearly correct *in vitro* coagulation abnormalities; however, it has been shown to be effective in controlling bleeding and reducing blood component requirements in cirrhotic patients with acute hemorrhage and in reducing bleeding following liver biopsy.

**Elective procedures**

Elective surgery in patients with liver disease, including liver transplantation and liver biopsy, should only be undertaken after careful patient assessment. The tests indicated in Table 3 are critical. Close collaboration between surgeon, hepatologist and hematologist is necessary. The transfusion laboratory should be warned of liver transplantation or major liver surgery. Blood components should be available in adequate quantities (red blood cells, platelets, fresh frozen plasma, cryoprecipitate and recombinant coagulation factors) and this will require prior arrangement with the hematologist/transfusion specialist and pharmacy.

Careful patient selection will help to minimize blood component requirement. Our own experience at the Royal Free Hospital has clearly demonstrated that patients with cirrhosis undergoing liver transplantation have a greater requirement for blood com-
ponent therapy than patients who do not have cirrhosis; amongst patients with cirrhosis those with primary biliary cirrhosis appear to have the least degree of hemostatic impairment. Requirements for blood component therapy within our own unit have declined significantly as a result of better patient selection. Indicative requirements for transplant are given in Table 5. The most significant reduction has been as a consequence of the regular use of aprotinin. It is clear that the use of aprotinin should be targeted towards patients who are at high risk for hemorrhage, and the risk:benefit ratio declines when it is used in patients at low risk of hemorrhage. Recombinant factor VIIa also has demonstrated utility in the elective management of liver biopsy, liver resection and liver transplantation.

### Side effects of treatment

Blood component treatment is expensive, may transmit a range of infections, and can reduce immunity. Our own unit has made substantial use of salvage devices that allow the infusion of the patient's own blood components following a filtration cycle. Pharmacologic agents may be associated with the risk of allergy and thrombosis. Most systematic studies have shown a low risk of complications with the use of recombinant factor VIIa. Recombinant erythropoietin is useful particularly for patients who are unable to accept blood transfusion therapy.

### References


Correspondence to: Dr Mehta, Consultant, Department of Hematology, Royal Free and University College School of Medicine, London