Hemostasis and thrombosis in patients with liver disease

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Importance of the liver in hemostasis

Synthesis of

- Coagulation factors
- Fibrinolytic proteins
- Thrombopoietin
Hemostatic alterations in liver disease

- Thrombocytopenia and platelet function defects
- Low levels of coagulation proteins & inhibitors
- Low levels of fibrinolytic proteins
- High VWF, FVIII, tPA, PAI-1
Causes of liver diseases?

- Cirrhosis
  - Cholestatic
  - Non-cholestatic
  - NAFLD/NASH

- Acute liver failure
  - Acetaminophen
  - Viral
  - Medication
- Elevated levels of VWF (and factor VIII)
- Elevated levels of tPA, PAI-1, nitric oxide and prostacyclin

- Low levels of coagulation factors and inhibitors
- Low levels of plasminogen and inhibitors of fibrinolysis
- Decreased levels of ADAMTS13
- Dysfibrinogenemia
- Thrombocytopenia and platelet function defects

- Thrombocytopenia
Hemostatic alterations in liver disease
Consequences for lab values

- Low platelet count
- Prolonged PT, APTT
Hemostatic alterations in liver disease

- Low platelet count
- Prolonged PT, APTT

Bleeding?
Bleeding complications in liver disease

Variceal bleeding – consequence of portal hypertension and local vascular abnormalities
Bleeding complications in liver disease

Procedural bleeding
Bleeding complications during liver transplantation

Transfusion. 1987 May-Jun;27(3):222-5:

“During the first 5 years (1981-1985) of the liver transplantation program in Pittsburgh, a total (preoperative, intraoperative, and postoperative) of 18,668 packed red cell units, 23,627 fresh-frozen plasma units, 20,590 platelet units, and 4241 cryoprecipitate units was transfused for the procedures (626 transplants). This represents 3 to 9 percent of the total of blood products supplied by the Central Blood Bank to its 32 member hospitals.”
Chapter 15

Hemostatic Defects in Liver and Biliary Tract Disease and Disorders of Vitamin K Metabolism
Oscar D. Ratnoff

A generalized bleeding tendency has long been recognized as a concomitant of protracted biliary tract obstruction, chronic hepatic disease, and the more severe forms of acute hepatitis, and it may contribute significantly to morbidity and mortality.\(^1\)\(^-\)\(^3\) Apparently spontaneous cutaneous purpura, epistaxis, and gastrointestinal, genitourinary, or gingival bleeding are disturbingly frequent. Impaired hemostasis may enhance bleeding from varices or peptic ulceration, and surgical procedures may be followed by devastating hemorrhage.
Dismantling the Myth of “Autoanticoagulation” in Cirrhosis: An Old Dogma Dies Hard


Excerpt

The reassessment of hemostasis in patients with chronic liver disease challenges the dogma that the major coagulopathy in these patients leads consistently to bleeding. Other changes that accompany chronic liver disease may restore the balance of anticoagulant and procoagulant effects. In certain circumstances, the risk of thrombotic events may be greater than the risk of hemorrhage. We speculate that drugs that are often regarded as contraindicated in patients with chronic liver disease may instead prove beneficial and should be tested in appropriate clinical trials.
Bleeding complications during liver transplantation
**Transfusion Rate for 500 Consecutive Liver Transplantations: Experience of One Liver Transplantation Center**

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**Background.** Orthotopic liver transplantation (OLT) has been associated with major blood loss and the need for blood product transfusions. During the last decade, improved surgical and anesthetic management has reduced intraoperative blood loss and blood product transfusions. A first report from our group published in 2005 described a mean intraoperative transfusion rate of 0.3 red blood cell (RBC) unit per patient for 61 consecutive OLTs. Of these patients, 80.3% did not receive any blood product. The interventions leading to those results were a combination of fluid restriction, phlebotomy, liberal use of vasopressor medications, and avoidance of preemptive transfusions of fresh frozen plasma. This is a follow-up observational study, covering 500 consecutive OLTs.

**Methods.** Five hundred consecutive OLTs were studied. The transfusion rate of the first 61 OLTs was compared with the last 439 OLTs. Furthermore, multivariate logistic regression was used to determine the main predictors of intraoperative blood transfusion.

**Results.** A mean (SD) of 0.5 (1.3) RBC unit was transfused per patient for the 500 OLTs, and 79.6% of them did not receive any blood product. There was no intergroup difference except for the final hemoglobin (Hb) value, which was higher for the last 439 OLTs compared with the previously reported smaller study (94 [20] vs. 87 [20] g/L). Two variables, starting Hb value and phlebotomy, correlated with OLT without transfusion.

**Conclusions.** In our center, a low intraoperative transfusion rate could be maintained throughout 500 consecutive OLTs. Bleeding did not correlate with the severity of recipient’s disease. The starting Hb value showed the strongest correlation with OLT without RBC transfusion.

**Keywords:** Liver transplantation, Transfusion, Phlebotomy, Antifibrinolytic, Cell saver, MELD score.
Thrombocytopenia is common

VWF is substantially elevated and compensates in part for the low platelet count
Thrombocytopenia is common

VWF is substantially elevated and compensates in part for the low platelet count
VWF multimers are cleaved by ADAMTS13

A deficiency of this protein leads to TTP
Reduced ADAMTS13 in cirrhosis
Caveats of routine diagnostic tests of hemostasis

Prothrombin time is only sensitive for VII, X, V, II, fg
Prothrombin time is insensitive for natural anticoagulants (AT, TFPI, PC/PS)

No protein C activation during TF-induced coagulation in plasma due to absence of thrombomodulin
Decreased levels of anticoagulants compensate for decreased levels of procoagulants

Hepatology 2005; 41: 553-558
Fibrinolysis in cirrhosis – concomitant decrease in pro- and antifibrinolytic factors

Clot lysis time (min)

Control  Mild  Moderate  Severe

Decreased permeability of plasma clots
Hemostatic balance

Healthy individual

Bleeding
Procoagulants

Thrombosis
Anticoagulants
Liver disease: Hemostatic rebalance

Patient with liver disease

Bleeding

Thrombosis

Procoagulants

Anticoagulants
Clinical evidence for rebalanced hemostasis in patients with liver disease

• Bleeding does occur in patients with cirrhosis. However, the most common bleeding complication – bleeding varices – is unrelated to hemostasis

• Liver transplantation – a major and lengthy surgical procedure – can be performed without any requirements for blood transfusion

• Patients with liver diseases are not ‘auto-anticoagulated’
Clinical consequences of ‘rebalanced hemostasis’ in patients with cirrhosis

• Prophylactic transfusion to correct routine laboratory abnormalities (plt count, PT, APTT) to prevent bleeding during invasive procedures is probably of little use

  • Effect of prophylactic transfusion prior to liver transplantation has never been proven
  • Complete correction almost never achieved
  • Transfusion has major side-effects
  • Fluid overload (fuels the fire)
  • Preoperative laboratory tests do not predict bleeding
  • Costs (major indication for FFP & platelets)
Thrombotic complications in cirrhosis

- Venous thrombosis
- Hepatic vascular diseases
- Coronary events
- Intrahepatic thrombosis
- ……
Indications for anticoagulant therapy

- Venous thrombosis
- Hepatic vascular diseases
- Coronary events
- Intrahepatic thrombosis
- .......

But: anticoagulants are underused as a result of the perceived bleeding risk
The anti-Xa assay underestimates LMWH mass in patients with cirrhosis
Enhanced anticoagulant potency of LMWH in patients with liver disease

![Graph showing % decrease in ETP for Control, Child A, Child B, and Child C](image-url)
Coagulation affects fibrogenesis in mice

Warfarin                    Control                 Factor Vleiden

Enoxaparin Prevents Portal Vein Thrombosis and Liver Decompensation in Patients With Advanced Cirrhosis

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Established and new-generation antithrombotic drugs in patients with cirrhosis – Possibilities and caveats

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In summary:

• Routine laboratory values do not accurately reflect the hemostatic status in cirrhosis

• The traditional concept that cirrhosis is associated with a hemostasis-related bleeding tendency is no longer valid

• Laboratory and clinical support for the concept of rebalanced hemostasis
  • Transfusion free transplantation
  • Normal hemostatic status in more sophisticated laboratory tests