Hemostasis in patients with impaired liver function

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Liver cirrhosis

Wikipedia:

As the disease progresses, complications may develop. Bruising and bleeding resulting from decreased production of coagulation factors. In some people, these may be the first signs of the disease.

British Society of Gastroenterology, October 2004
Guidelines on the use of Liver Biopsy in Clinical Practice

* platelet number < 60,000: platelet transfusion?
* platelet number < 40,000: no normal biopsy
* PT > 4 sec: fresh frozen plasma?
* PT > 6 sec: no normal biopsy

Risk of bleeding?
How strong is the risk of bleeding?

The risk of major intraperitoneal bleeding after liver biopsy is 0.08-0.7%, based on different hospital series.

Overall mortality rate 0.01-0.4%


Consequences of liver diseases for laboratory diagnostics:

- Low platelet count
- Prolonged PT (INR) & aPTT

Are diagnostic hemostasis tests telling the whole story?
The liver plays an important role in hemostasis.

- It is the site of production of many of the coagulation factors and their inhibitors.
- It is the site of vitamin K-dependent modulation of clotting factors.
- It is responsible for clearance and degradation of factors, factor-inhibitor complexes.
- It is the site of synthesis of thrombopoietin.
Hemostatic balance
Liver and platelets

Mild to moderate thrombocytopenia (50,000 – 150,000/µL)

- Increased platelet sequestration in the spleen
- Decreased production of thrombopoietin
- Reduced half life
- Auto-immune induced
- Low grade DIC
- Folic acid deficiency (alcohol-induced cirrhosis)

Platelet function defects.

- Acquired storage pool disease
- Decreased levels of arachidonic acid
- Increased fibrinolysis (plasmin cleavage of platelet receptors)
- Increased NO and prostacyclin synthesis
- Reduced hematocrit
Primary hemostasis in patients with cirrhosis

• Thrombocytopenia is common

• Thrombocytopathy has been described

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

Hepatology. 2006; 44:53-61
Primary hemostasis

Control

Patient

High VWF compensates for the low platelet count present in patients with cirrhosis

Hepatology. 2006; 44:53-61
Reduced ADAMTS-13 in chronic and acute liver failure


High vWF and low ADAMTS-13: a misbalance

Reduced ADAMTS13 in acute liver failure is associated with outcome

Primary hemostasis and liver failure

- Low platelet count and loss of function does not lead to impaired primary hemostasis because these defects are compensated by high von Willebrand factor levels and low ADAMTS-13 activity.

- How about secondary hemostasis?
• The clotting times of the APTT and PT are sensitive for variations in the levels of coagulation factors but they are insensitive for variations in coagulation inhibitors such as antithrombin and protein C.

• Liver cirrhosis results in a decrease of coagulation factors and inhibitors.

• APTT and PT (INR) are not suitable to monitor the hemostatic balance in patients with liver diseases.

• A better test in the thrombin generation test.
Evidence of Normal Thrombin Generation in Cirrhosis Despite Abnormal Conventional Coagulation Tests

Armando Tripodi, Francesco Salerno, Veena Chantarangkul, Marigrazia Clerici, Massimo Cazzaniga, Massimo Primignani, and Pier Manuccioni Mannucci

Hepatology 2005; 41: 553-558
Thrombin generation has one important drawback, it lacks the participation of the vessel wall.

Add thrombomodulin
Thrombin generation

- No difference between cirrhotic patients and healthy volunteers
- Cirrhotic patients are resistant to active protein C
Addition of thrombomodulin

Thrombin generation in plasma of cirrhotic patients is comparable to thrombin generation in plasma of healthy individuals in the presence of thrombomodulin.

FVII ~ 5%
FV ~ 15%
PC ~ 5%
AT ~ 35%
INR ~ 3

P<0.001
ns

Secondary hemostasis and liver failure

- Decreased levels of procoagulant proteins are accompanied by decreased levels of natural anticoagulant proteins.
- In particular patients with liver disease are resistant to the action of thrombomodulin
- The net changes results in a rebalanced, but functional system.
- A prolongation of the APTT and PT do not predict an increased risk of bleeding
Fibrinolysis

- No evidence for increased plasma fibrinolytic potential in cirrhosis
- The reduction of anti-fibrinolytic factors in cirrhosis is compensated by a concomitant reduction in pro-fibrinolytic factors

*Lisman et al. Gastroenterology 2001; 121: 131-139*
Increased levels of D-Dimers → a sign of DIC?

DIC: VIII ↓, Cirrhosis: VIII ↑

Thrombin-antithrombin levels are also increased.

No correlation with PVT

The levels of D-Dimers and TAT might be increased due to a decreased clearance in the liver
Hemostatic balance

Normal liver

Cirrhotic liver
Hemostatic balance

Patient with cirrhosis

Renal failure, infection, .....  

Altered blood flow, endothelial activation, .....  

Bleeding  
Thrombosis  

Procoagulants  
Anticoagulants
Bleeding
Traditionally, perioperative bleeding complications were a major concern during liver transplantation.

A mean (SD) of 0.5 (1.3) RBC unit was transfused per patient for the 500 OLTs.

79.6% of the patients did not receive any blood product.
Liver transplantation

Coagulation Defects Do Not Predict Blood Product Requirements During Liver Transplantation

Luc Massicotte,1,5 Danielle Beaulieu,1 Lynda Thibeault,2 Jean-Denis Roy,1 Denis Marleau,3 Réal Lapointe,4 and André Roy4

- There was no link between coagulation defects and bleeding or RBC or plasma transfusions.
- It is neither useful nor necessary to correct coagulation defects with plasma transfusion before liver transplantation

Transplantation 2008; 85: 956–962
Bleeding

Gastrointestinal tract
• Most frequent, 80-90% of bleeding episodes
• 30% fetal
• Esophageal or gastric varices
• Major determinant: portal hypertension
• Hemostasis: limited predictive value (tPA, D-dimers)

Intracerebral haemorrhage
• Rare (0.8%)
• Non-cirrhotic alcohol liver disease.

Liver biopsy
• Major bleeding is not a frequent complication.
• Neither PT nor aPTT and platelet number are predictors.
• The bleeding risk in patients with acute liver failure was estimated to be higher than that of cirrhosis

• However, there has been an unexplained decline in severe bleeding over the past 40 years.

• Increased bleeding risk is associated with bacterial infections.

• Prophylactic administration of antibiotics reduced the risk of bleeding

• Increased circulating heparine like molecules?
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 cirrhosis 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)
What to do prior to an invasive procedure?

- Bleeding history! Consider infection and renal failure
- PT/INR does not predict bleeding – prophylactic plasma transfusion is not indicated!
- A minimal platelet count may be required, but prophylactic transfusion is probably not indicated
- Wait-and-see (perhaps unless bleeding may result in irreversible damage)
- Avoid fluid overload
Thrombosis
Portal vein thrombosis

- PVT is often asymptomatic.
- 15% of patients have an overt PVT at the time of liver transplantation, the incidence of occult PVT is even higher.
- PVT is associated with portal hypertension, ascites, encephalopathy and intestinal ischemia.
- It is not known whether the pathophysiology of PVT resembles DVT (fibrin rich or platelet rich)
Hepatic artery thrombosis

Observed after surgery
   early and long term post surgery

More often after metabolic liver disease
   (acute intermittent porphyria; familial amyloidotic polyneuropathy)

Increased risk if graft carries a thrombophilia mutation

Increased risk with CMV infection

Patient with history of PVT
Peripheral thrombosis

- All patients with underlying coagulopathy were excluded in clinical trials studying the risk of VTE → extremely cautious to draw conclusions

- Single center studies: between 0.5 and 6.3%

- Exposure to other risk factors
  - Cancer
  - Older age
  - Surgical procedures
  - Inactivity
  - Hospitalization

Coagulopathy is not protective for VTE in patients with cirrhosis
Vascular events after liver transplantation: a long-term follow-up study

Maarten A. J. P. Borg,¹ Egbert-Jan van der Wouden,¹ Wim J. Sluiter,² Maarten J. H. Slooff,³ Elizabeth B. Haagsma¹ and Arie P. van den Berg¹

• 311 patients who survived the first year after transplantation were followed for 6.2 years (1-20)

• 21% of the deaths were due to VTE

• Risk factors: hypertension, age, smoking, renal failure and hypercholesterolemia

• Adequate treatment was associated with a reduced risk of VTE
Thrombosis after OLT

- Both early and late HAT occur after liver transplantation
- Patients transplanted for metabolic liver disease have a higher risk for HAT than patients with cirrhosis or fibrosis
- Patients with thrombophilic mutations have a higher risk
- CMV infection is associated with a higher risk
- Previous PVT
- A single study: aspirin reduces the risk of HAT >80%
Treatment
Chronic liver disease patients are not protected against venous and arterial thrombosis.

There are some studies suggesting that chronic liver disease has a two-fold increased risk of venous thrombosis.

Patients with non-alcoholic fatty liver disease have an increased risk of arterial thrombosis.

There is not much experience in treating cirrhotic patients with thrombosis and there are no established guidelines.
Anti-platelet therapy

Aspirin

• Cirrhosis has been listed as contra-indication for aspirin use
• However, the current evidence has shown that aspirin is relatively safe in patients without varices.
• Varices are a contraindication for the use of aspirin

P2Y12 blockers

• P2Y12 blockers often require metabolic activation by the liver, making the pharmacokinetics unpredictable
• Prasugrel can be used according to the package insert
• Ticagrelor is cleared by the liver
What should the target INR in a patient with liver disease (and already prolonged INR) be???

Two studies: unacceptable high level of bleeding complications
In a small randomized controlled trial, a 12-month course of enoxaparin was safe and effective in preventing PVT in patients with cirrhosis.

Enoxaparin appeared to delay the occurrence of hepatic decompensation and to improve survival.
The anti-Xa assay underestimates LMWH mass in patients with cirrhosis.

Monitoring LMWH

Enhanced anticoagulant potency of LMWH in patients with liver disease

Dabigatran: direct thrombin inhibitor

- Patients with normal liver function: Increase of lower GI bleedings
- Cleared in kidney (80%)
- Package insert: liver disease is not explicitly contraindicated

Rivaroxaban: direct factor Xa inhibitor

- Associated with a higher risk of GI bleeding in patients with adequate liver function
- Cleared by kidney (66%) and liver (34%)
- Package insert: do not use in Child B and C patients
NOACs in liver disease?

Anti-Xa or anti-IIa assays appear reliable in patients with liver disease

NOACs in liver disease?

Enhanced anticoagulant potency of Dabigatran, but decreased anticoagulant potency of Rivaroxaban in patients with liver disease

PlosOne 2014, in press
Platelets
Platelets & liver transplantation

Dense Granules
- Platelet agonists
  - ADP, ATP
  - Mg
  - Ca^{2+}
  - Histamine
  - Serotonin

Alpha Granules
- Cell Mitogens
  - PDGF
  - TGFβ
  - EGF
  - bFGF
  - VEGF
  - IGF
  - Interleukin β

Platelet Aggregation
- Hemostatic factors/Coagulation Factors
  - Factor V, VIII, XI, XII
  - Kininogen
  - Fibrinogen
  - Plasminogen
  - Protein S
  - PAI 1

Platelet Activation
- Adhesion Proteins
  - Fibrinogen
  - Fibronectin
  - vWF
  - Thrombospondin
  - Vitronectin

Platelet Specific
- Antigen Receptors
  - GPIV
  - Vitronectin Receptor
  - P-selectin
  - GPIb/IIIa
  - GPIb/IX
  - PECAM

Chemokines
- Leukocyte Recruitment
  - IL-1β
  - CD40L
  - RANTES
  - MIP-1α
  - PF4
  - IL-8
  - ENA-78

Lysosomes
Suppression of fibrosis


Role of platelets in chronic liver disease and acute liver injury.

Nowatari T, Murata S, Fukunaga K, Ohkohchi N.
• Median platelet counts in patients who were still alive 90 days after surgery (survivors, n = 340) and in patients who died within 90 days after surgery (non-survivors, n = 45).

• Tissue repair was delayed after acute liver injury in platelet-depleted mice

  Peereboom et al. Liver Transplantation 2008; 14: 923-931
  Nocito et al. Hepatology 2007; 45:369-376
Platelet and red cell transfusions are related to mortality after liver transplantation

De Boer et al, Anesth Analg 2008;106:32-44
Platelet and red cell transfusions are an independent predictor of mortality after liver transplantation.
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
- Thrombotic risk > bleeding risk
- Studies on optimal anticoagulant management are urgently required