Introduction
Massive blood loss requiring allogenic blood product transfusion has been a major problem during liver resection and transplantation surgery. The transfusion of red blood cell units (RBCs) and plasma has been adversely linked to 1-year survival rates. In a series of 1,085 consecutive cases undergoing hepatic resection surgery, total blood loss and the number of liver segments resected were the only independent predictors of morbidity and morality. Improved surgical and anaesthetic techniques have resulted in a dramatic reduction of blood product requirements during orthotopic liver transplantation (OLT) and liver resection surgery compared to historical controls. Recent publications report that between 17.5% and 81% of OLT operations and >90% of hepatic resections can now be performed without red blood cell transfusions. In both groups, reduction in blood transfusions has led to improved outcome. Severe bleeding still occurs in a minority of cases and efforts to define clinical and blood test predictors for major bleeding during liver surgery remain elusive.

Excessive bleeding during liver surgery can be due to surgical factors, haemostatic problems due to liver disease or other causes and poor anaesthetic technique, as highlighted in Table I.

Table I: Causes of bleeding in patients undergoing liver surgery

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<th>Surgical factors</th>
<th>Liver disease</th>
<th>Anaesthetic factors</th>
<th>Miscellaneous</th>
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<td>• Nature of surgery</td>
<td>• Coagulation defects</td>
<td>• Elevated central venous pressure</td>
<td>• Renal dysfunction</td>
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<td>• Previous upper abdominal surgery</td>
<td>• Thrombocytopenia</td>
<td>• Hypothermia</td>
<td>• Sepss</td>
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<td>• Collateral circulation due to portal hypertension</td>
<td>• Thrombocytopenia</td>
<td>• Acidosis</td>
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<td>• Fibrolisis</td>
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Surgical factors
Two key surgical factors have contributed to the reduction in blood transfusion requirements during major liver surgery. Firstly improved understanding of the segmental anatomy of the liver as described by Couinaud has allowed relatively bloodless, anatomically based resections and secondly, the use of vascular occlusion techniques to reduce blood loss during dissection. A number of new devices such as the Cavitron Ultrasonic Surgical Aspirator (CUSA®), Hydro-jet and a dissecting sealer have been marketed to facilitate parenchymal transection during liver surgery. A recent meta-analysis of randomised controlled trials comparing these devices to the traditional crush-clamp technique however was unable to demonstrate a benefit. Factors increasing the risk of bleeding during liver surgery include collateral circulation due to portal hypertension, previous upper abdominal surgery, the presence of cirrhosis or sepsis, coagulopathies, raised central venous pressure (CVP), acidosis and hypothermia.

Liver disease and coagulation
The liver plays a key role in haemostasis. Parenchymal cells synthesise most of the factors controlling coagulation and fibrinolysis and the liver's reticulo-endothelial system plays an important modulatory role through the clearance of breakdown products of coagulation and fibrinolysis.

Patients undergoing hepatic resection surgery are more likely to have preserved liver function compared with those undergoing OLT. The latter usually have either end stage liver disease (ESLD) due to cirrhosis or fulminant liver failure. Steatosis due to obesity is an increasing problem in the USA and together with cirrhosis increases the risk of reperfusion injury during hepatic resection surgery, limiting vascular occlusion times and the volume of liver that can be safely resected.

Coagulation tests are a measure of the synthetic function of the liver and parallel the degree of parenchymal liver damage in patients with acute or chronic liver disease. The PT/INR is a useful prognostic test in patients with liver dysfunction hence its incorporation into prognostic scoring systems such as the Child-Pugh-Turcotte (CPT) and the Model for End Stage Liver Disease (MELD). Conventional tests of the clotting cascade such as the PT/INR, APTT and bleeding time have however been shown to correlate poorly with procedure related bleeding in patients with cirrhosis. The reduction in clotting factors represented by increased aPTT and INR is thought to be counterbalanced by a parallel reduction in natural anticoagulants such as protein C, protein S and antithrombin. Thrombin generation in cirrhosis, when assessed with assays that include thrombomodulin (a protein C activator), is normal.

Impaired haemostasis in patients with end stage liver disease (ESLD)
Causes of haemostatic abnormalities in ESLD are discussed below and summarised in Table II.

Coagulopathy
A cardinal feature of cirrhosis is the development of a coagulopathy due to a decrease in the production of clotting factors as a result of reduced hepatocyte synthetic function. Concomitant malnutrition, malabsorption or cholestasis can aggravate the coagulopathy by causing a deficiency of vitamin K and vitamin K dependent factors (Factors II, VII, IX, X, protein C and protein S). Factor VIII and von Willebrand factor (vWF) are synthesised outside the liver and levels are often increased in cirrhosis.

Systemic fibrinolysis
Low grade fibrinolysis, although common in patients with ESLD is not usually associated with increased bleeding. It is due to decreased clearance of tissue plasminogen activator (tPA) and impaired hepatic synthesis of fibrinolytic inhibitors such as thrombin activatable fibrinolysis inhibitor (TAFI), by the liver. Major surgery may stimulate the release of large amounts of tPA from injured tissues, overcoming the body's antifibrinolytic mechanisms and resulting in hyperfibrinolysis and bleeding.
Mechanisms are complex and include impaired clearance of active clotting factors, decreased synthesis of coagulation inhibitors, release of procoagulants from injured hepatocytes and the entry of endotoxins into the portal circulation.

**Hypercoagulability**

Patients with chronic liver disease are not protected from thrombotic events despite the prolongation of conventional coagulation tests. They may generate normal or even high levels of thrombin and have increased levels of factor VIII and vWF. The risk of portal vein thrombosis is further increased in cirrhotic patients carrying prothrombotic mutations such as factor V Leiden.

**Anaesthetic factors**

The anaesthetist plays an important supporting role in reducing bleeding during major hepatic surgery. Anaesthetic technique should be aimed at maintaining organ perfusion and avoiding hepatotoxic drugs.

During liver resection surgery, inflow occlusion techniques are frequently used together with a low CVP strategy, to reduce blood loss. Lowering the CVP augments venous drainage from the liver and reduces parenchymal bleeding by reducing back pressure from the hepatic veins. Low CVP strategies are effective at reducing blood loss.

Fibrinolysis may be detected by decreased levels of fibrinogen and 2-antiplasmin, increased D-dimers in blood, and by a decreased clot lysis index together with the characteristic rat-tailed pattern seen on viscoelastic tests of coagulation such as the Thrombelastogram (TEG®) or ROTEM®.

**Thrombocytopenia**

Although mild to moderate thrombocytopenia occurs commonly in patients with ESLD, spontaneous bleeding is uncommon, probably due to high levels of vWF which support platelet adhesion. Mechanisms for thrombocytopenia include increased sequestration of platelets due to hypersplenism caused by portal hypertension, impaired platelet production due to decreased synthesis of thrombopoietin by the liver and immune and non-immune platelet destruction. Additional causes include folate deficiency, alcohol, heparin, disseminated intravascular coagulation (DIC) and sepsis. Following successful OLT in cirrhotic patients, thrombopoietin increases and platelet counts return to normal.

**Platelet function defects**

Qualitative abnormalities of platelet function occur in many patients with ESLD as evidenced by a prolonged bleeding time and impaired tests of platelet aggregation. This occurs even in patients with adequate platelet numbers. A multifactorial aetiology is probable. Mechanisms attributed include the presence of circulating platelet inhibitors (fibrin degradation products and D-dimers), plasmin induced degradation of platelet receptors, dysfibrinogenemia, a deficiency of platelet GP1b receptors, drugs and excess nitric oxide synthesis. Nitric oxide, produced by vascular endothelial cells, inhibits platelet adhesion and aggregation. Patients with cirrhosis and concomitant renal failure may develop ureamic thrombocytopenia.

**Disseminated intravascular coagulation (DIC)**

Mechanisms are complex and include impaired clearance of activated clotting factors, decreased synthesis of coagulation inhibitors, release of procoagulants from injured hepatocytes and the entry of endotoxins into the portal circulation.

<table>
<thead>
<tr>
<th>Haemostatic defect</th>
<th>Possible mechanism</th>
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<tr>
<td>Impaired coagulation</td>
<td>Reduced synthesis of clotting factors&lt;br&gt;Vitamin K deficiency&lt;br&gt;Dysfibrinogenemia</td>
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<tr>
<td>Systemic fibrinolysis</td>
<td>Impaired clearance of tPA and fibrinolytic enzymes&lt;br&gt;Reduced synthesis of 2-antiplasmin and TAFI&lt;br&gt;Resorption of ascitic fluid into circulation</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Sequestration due to splenomegaly&lt;br&gt;Impaired synthesis of thrombopoietin&lt;br&gt;Immune destruction&lt;br&gt;Disseminated intravascular coagulation&lt;br&gt;Others (drugs, folate deficiency, alcohol, etc)&lt;br&gt;Sepsis</td>
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<tr>
<td>Impaired platelet function</td>
<td>Circulating platelet inhibitors&lt;br&gt;Excess nitric oxide production&lt;br&gt;Deficiency of glycoprotein receptors&lt;br&gt;Defective platelet signal transduction&lt;br&gt;Impaired thromboxane A2 synthesis&lt;br&gt;Uraemia</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation</td>
<td>Release of procoagulants from injured hepatocytes&lt;br&gt;Impaired clearance of active clotting factors&lt;br&gt;Reduced synthesis of coagulation inhibitors&lt;br&gt;Endotoxins in portal circulation&lt;br&gt;Entry of ascitic fluid into systemic circulation</td>
</tr>
<tr>
<td>Hypercoagulability</td>
<td>Genetic mutations&lt;br&gt;Elevated factor VIII&lt;br&gt;Reduction in natural anticoagulants</td>
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tPA = tissue plasminogen activator, TAFI = thrombin activatable fibrinolysis inhibitor
d) Tests are performed at 37°C rather than at the patient's temperature.

Viscoelastic coagulation tests such as the TEG®/ROTEM® overcome many of these problems in that they allow rapid, point of care, dynamic monitoring of clot generation, platelet function and clot lysis in whole blood. They do not provide information relating to the interaction between platelets and vascular endothelium and are therefore unable to demonstrate the effect of aspirin on bleeding. Pioneering work by Kang et al demonstrated the value of TEG® analysis in directing blood product transfusion and reducing the requirement for blood products during OLT. 20

Transfusion of blood products
Massicotte reported a wide variation in transfusion habits by individual anaesthesiologists in their liver transplantation programme.2 Evidence-based guidelines for blood product transfusion do not exist. Packed RBCs are usually transfused to target a haemoglobin level of 8–10 g/dl with variations in transfusion requirements. A meta-analysis of randomised controlled trials investigating the use of FFP.24 The study found no evidence that patients receiving acid (TA) significantly reduced RBC transfusion requirements. Antifibrinolytics not cost effective.23 The authors concluded that the routine use of fibrin glue was sealants did not reduce blood loss or transfusion requirements. The authors concluded that the routine use of fibrin glue was not cost effective. 21

Pharmacological management of bleeding during liver surgery
Topical haemostatic agents
Topical agents are used by some surgeons to stimulate haemostasis on the raw surface of the liver after parenchymal resection. These are either fibrin sealants that mimic coagulation, agents that provide a matrix for endogenous coagulation such as cellulose sponges or a combination of the two. A Cochrane review published in 2003 confirmed the efficacy of fibrin sealants.22 In contrast a recent randomised controlled trial in 500 patients undergoing partial hepatic resection found that fibrin sealants did not reduce blood loss or transfusion requirements. The authors concluded that the routine use of fibrin glue was not cost effective. 23

Antifibrinolytics
A meta-analysis of randomised controlled trials investigating the safety and efficacy of antifibrinolytic agents in liver transplantation demonstrated that both aprotinin and tranexamic acid (TA) significantly reduced RBC transfusion requirements. Aprotinin but not TA significantly reduced intraoperative use of FFP.24 The study found no evidence that patients receiving antifibrinolytic agents developed intraoperative thromboembolism during OLT.25 Mangano’s 2006 paper describing that platelet transfusion during OLT should be reserved for thrombocytopenic patients who are actively bleeding rather than as prophylaxis.25

Recombinant factor VIIa
Several randomised clinical trials investigating the use of recombinant factor VIIa in cirrhotic and non-cirrhotic patients undergoing partial liver resection or OLT have failed to demonstrate a clinically significant difference in blood loss or transfusion requirement. It has been suggested that this drug should be reserved as a “rescue therapy” to control bleeding where other therapies have failed.

Conflict of interest
We declare that we have no financial or personal relationships which may have inappropriately influenced us in writing this paper.

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References: