Pathophysiology and management of hemostatic alterations in cirrhosis and liver transplantation
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CHAPTER 11

Summary
Changes in the hemostatic system frequently occur in patients with advancing chronic liver disease, and as a consequence patients with chronic liver disease may suffer from both bleeding- and thrombotic complications (1). The aim of this thesis was to investigate and summarize the hemostatic function in patients with chronic liver disease prior to, during, and after orthotopic liver transplantation (OLT), and to provide insight into old and new hemostatic agents that might be helpful to decrease morbidity and mortality related to the hemostatic derangements in these patients.

Chapter 1 provides a general introduction to this thesis, including the background and aim of each chapter.

Chapter 2 describes the effect of a single intravenous bolus of 1-deamino-8-D-arginine vasopressin (DDAVP) on hemostatic indices in plasma from patients with cirrhosis and patients with hemophilia. The aim was to investigate whether a single bolus administration of DDAVP had any prohemostatic effect in the plasma from patients with cirrhosis that could explain the hemostatic efficacy described in some clinical studies. Patients with Child Pugh B and C cirrhosis, and patients with mild hemophilia were given a single intravenous bolus of DDAVP. Prior to, and at several time points following the bolus, plasma samples were collected. In these samples, levels of von Willebrand factor (VWF), VWF propeptide, Factor VIII (FVIII), and ADAMTS13 were measured, whereas VWF multimers and functional VWF-dependent platelet adhesion were determined in the samples pre- and 1 hour after DDAVP administration. Levels of VWF, VWF propeptide, and FVIII levels increased in patients with hemophilia after DDAVP administration, while patients with cirrhosis only showed a significant increase in VWF propeptide and an increase in FVIII levels that did not reach statistical significance. The proportion of high molecular weight VWF multimers and VWF-dependent platelet adhesion increased in patients with hemophilia one hour after DDAVP administration, but did not change in the patients with cirrhosis. Levels of ADAMTS13 were unaffected in both patient groups. While DDAVP is prophylactically used by some centres to prevent bleeding during invasive procedures in patients with cirrhosis, our study showed a lack of relevant hemostatic effects of DDAVP in patients with cirrhosis, questioning its use as a pro-hemostatic agent in these patients.

Chapter 3 describes a study in which we aimed to investigate whether anticoagulant drugs in cirrhotic patients have different potencies compared to healthy controls and whether dose adjustments are required in this patient population. Thrombin generation assays were performed before and after in vitro addition of a fixed dose of unfractionated heparin (UFH), low molecular weight heparin (LMWH), fondaparinux, dabigatran, and rivaroxaban. A strongly enhanced anticoagulant effect was found in patients with cirrhosis after addition of the direct thrombin inhibitor dabigatran (72.6% reduction in endogenous thrombin potential in patients compared to 12.8% reduction in controls). The enhanced anticoagulant potency of dabigatran was proportional to the sever-
Addition of UFH and LMWH also led to an enhanced anticoagulant effect in patients with cirrhosis as compared to controls, however this effect was less pronounced. Fondaparinux and rivaroxaban demonstrated a reduced anticoagulant effect in patients with cirrhosis as compared to controls. These findings demonstrate that the anticoagulant potencies of clinically approved drugs vary significantly between patients with liver disease and healthy individuals, and also may vary between different subgroups of patients. Drug specific dose adjustment may thus be required in patients with cirrhosis based on altered pharmacokinetics and altered anticoagulant potency.

Chapter 4 describes a study in which we aimed to investigate the accuracy of anti-Xa assays in monitoring antithrombin (AT-) dependent and –independent anticoagulant drugs in plasma from patients with cirrhosis. Anti-Xa levels were measured after in vitro addition of fixed doses of various anticoagulant drugs in plasma from patients with cirrhosis and controls. Substantially reduced levels of anti-Xa were found when AT-dependent anticoagulant drugs were added to the plasma of patients with cirrhosis as compared to controls. LMWH (0·2 U/ml) had the poorest recovery in plasma from patients with cirrhosis (0.13 ± 0·06 U/ml, compared to 0.23 ± 0·03 U/ml in controls (p < 0.0001)), followed by UFH and fondaparinux. The recovery of rivaroxaban and dabigatran however was identical between patients and controls. These data suggest that the anti-Xa assay substantially underestimates drug levels of AT-dependent anticoagulant drugs in patients with cirrhosis. Direct factor Xa and IIa inhibitors, however, may be monitored through the respective anti-Xa and anti-IIa assays in patients with cirrhosis.

Blood loss during liver transplantation is dependent on several factors including the surgical technique, patient characteristics such as prior surgery and type of liver disease (including the severity of hemostatic derangements and portal hypertension), as well as the anesthesiological management during the transplantation. In Chapter 5 causes of bleeding during liver transplantation, strategies to prevent blood loss and treatment possibilities are reviewed. Despite the prolonged prothrombin time (PT) and decreased platelet count, there is increasing evidence for a rebalanced hemostatic system in patients with chronic liver disease. During liver transplantation the hemostatic status appears to remain in balance when tested by more sophisticated laboratory tests (2, 3). Clinical experience suggests that portal hypertension, fluid overload, and a hyperdynamic circulation are much more important determinants of bleeding than a dysfunctional hemostatic system. Volume contraction, achieved by a restrictive transfusion policy, therefore may be critical in minimizing blood loss during liver transplantation, and preoperative correction of PT and platelet count with high volume blood products may work counterproductive (4-7). Transfusion of blood products also significantly increases morbidity and mortality in patients undergoing OLT (8). During OLT, on-demand use of antifibrinolytics may be considered, especially when there is evidence of hyperfibrinolysis on thromboelastography in the presence of ongoing bleeding. Also, the use of
recombinant FVIIa may be considered, but little data on efficacy and safety are available. Additional studies on the optimal management of intractable bleeding during liver transplantation are required.

**Chapter 6** describes a study that investigated the effect of the discontinuation of aprotinin on blood loss and transfusion requirements during OLT. From 2000 until 2007 aprotinin was the antifibrinolytic drug of choice in the University Medical Center of Groningen and it was used prophylactically in most patients undergoing OLT. Due to safety concerns in the field of cardiac surgery the drug was discontinued in 2007, and from there on hardly any patient received antifibrinolytic therapy during OLT. In this study, data from the aprotinin era (2000-2007) as well as the post-aprotinin (2007-2013) era were analyzed to determine whether the discontinuation of aprotinin had caused an increase in blood loss and red blood cell (RBC) transfusion during OLT. The proportion of patients without any RBC transfusion decreased from 39% in the aprotinin era to 21% in the post-aprotinin era (p<0.001). The median amount of RBC transfusion increased from 2 (IQR 0-6) in the aprotinin era to 4 units (IQR 1-9) in the post-aprotinin era (p<0.001). In a multivariable logistic regression analysis, the need for RBC transfusion was significantly higher in patients that did not receive aprotinin during OLT compared to patients who did receive aprotinin. These results emphasize the role of hyperfibrinolysis in blood loss during OLT and plea for further investigation and reconsideration of prophylactic use of aprotinin or other antifibrinolytic drugs in patients undergoing OLT.

**Chapter 7** describes the protocol of an ongoing multicenter randomized controlled trial investigating the hemostatic efficacy of prothrombin complex concentrates (PCC). Due to the fact that this is a low volume product that contains balanced amounts of both pro-, and anticoagulant proteins, PCC might be helpful in reducing blood loss during OLT by strengthening both sides of the hemostatic axis without the risk of aggravating portal hypertension. Preliminary results are expected in the first quarter of 2017.

**Chapter 8** describes a study that investigated the contribution of portal hypertension to blood loss and RBC transfusion requirements in OLT. Established serum markers for portal hypertension, VWF and soluble CD163 (sCD163), were measured in preoperatively collected serum samples of 168 adult patients undergoing primary OLT between 1998 and 2012. Levels of VWF and sCD163 correlated with model of end-stage liver disease (MELD) score (r 0.414; p<0.001 and r 0.382; p<0.001, respectively). Patients with VWF or sCD163 levels above the median had significantly increased blood loss and were more likely to receive RBCs compared to patients with low VWF or sCD163 serum levels (odds ratio 3.450 [95% CI 1.703-6.99] and 2.276 [95% CI 1.146-4.519] respectively). Patients with the combination of high VWF and high preoperative INR had the highest amount of blood loss and RBC transfusion during OLT. These results indicate that portal hypertension is a significant contributor to blood loss and RBC transfusion during OLT, and emphasize the importance of adequate hemodynamic management during OLT.
In Chapter 9 we discuss and summarize evidence for a hypercoagulable state in the liver transplant recipient. While the hemostatic status of the patients with chronic liver disease and the patient during and directly after OLT has been studied and described, very little is known of the long-term hemostatic status of the liver transplant recipient. Complications such as the postoperative hepatic artery thrombosis have mainly been ascribed to technical difficulties during OLT. However, there is laboratory evidence for a contribution by a hypercoagulable hemostatic system including high levels of the platelet adhesive protein von Willebrand factor with low levels of its regulator ADAMTS13, an increased potential to generate thrombin, and a temporary hypofibrinolysis (3,9-11). Clinical evidence for the contribution of the hemostatic system in postoperative thrombosis includes a higher risk for deep venous thrombosis and cardiovascular disease, and death due to cardiovascular disease in patients with various acquired thrombotic risk factors after OLT (12-15). Although data on efficacy of anticoagulant therapy after liver transplantation are scarce, one study has shown a tremendous decrease in the risk for late hepatic artery thrombosis after antithrombotic therapy with aspirin (16). These findings suggest that antihemostatic therapy in prevention or treatment of thromboembolic complications after liver transplantation may be relevant. Studies on efficacy and safety of these interventions are required as many of the thrombotic complications have a pronounced negative impact on graft and patient survival.

Chapter 10 describes a study that investigated the hemostatic status of the liver transplant recipient one year after OLT. We aimed to determine whether liver transplant recipients have a hypercoagulable hemostasis that could (partially) explain the increased incidence of vascular complications both early and late after OLT. Indices of hemostasis were measured in plasma from 15 liver transplant recipients one year after OLT with normal liver function and no evidence of disease recurrence, and in plasma from 30 healthy volunteers. Patients one year after liver transplantation had significantly elevated plasma levels of VWF. Thrombin generation, as assessed by the endogenous thrombin potential, was decreased in patients, which was associated with increased plasma levels of the natural anticoagulants antithrombin and tissue factor pathway inhibitor. Plasma fibrinolytic potential was significantly decreased in patients and correlated inversely with levels of plasminogen activator inhibitor-1. These results demonstrate that one year after liver transplantation, liver transplant recipients have a dysregulated hemostatic system characterized by elevation of plasma levels of endothelial-derived (but not of liver-derived) proteins. Increased levels of VWF and decreased fibrinolytic potential may (in part) be responsible for the increased risk for vascular disease seen in liver transplant recipients.
REFERENCES


