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Blood platelets in liver transplantation

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Chapter 1 provides a short introduction on primary hemostasis in general and the changes in primary hemostasis in patients with severe liver disease and during liver transplantation in particular. Furthermore, the aims of this thesis are discussed. This thesis evaluates the different aspects of the role of blood platelets and primary hemostasis during and after liver transplantation. Furthermore, sudden thrombocytopenia after liver transplantation, the influence of prothrombotic gene polymorphisms on postoperative hepatic vessel thrombosis, and the impact of exogenous, transfused platelets on outcome, are discussed in this thesis.

Chapter 2 gives a review of literature on the role of blood platelets in liver transplantation. Blood platelets are believed to possess both beneficial as well as detrimental effects during liver transplantation. A certain amount of platelets is required to maintain hemostasis, and platelet transfusions may in some cases be unavoidable during liver transplantation. However, platelets have been shown to contribute to ischemia and reperfusion injury of the liver graft (1;2) and platelet transfusions have been associated with adverse outcome after liver transplantation (3). Although platelets are potentially harmful by contributing to ischemia and reperfusion injury, platelets also secrete substances such as serotonin, which may assist in the repair of ischemic damage after liver transplantation (4). This hypothesis is based on experimental studies that have shown that platelet-derived serotonin is involved in liver regeneration after partial liver resection (4). Detrimental effects of platelets in the period following transplantation concern thrombotic complications such as hepatic artery thrombosis (HAT) and systemic arterial disease including myocardial infarction and stroke (5). Due to the central role of platelets in arterial thrombosis, anti-platelet therapy seems an attractive strategy to avoid these complications after liver transplantation.

Chapter 3 describes the results of an observational study on platelet function during and after liver transplantation. Based on the literature, we hypothesized that platelets would be activated during the course of transplantation, and that platelet function would

deteriorate as a result of platelet activation and proteolysis of platelet receptors by plasmin following reperfusion (6;7). Surprisingly, in this study we found no evidence for platelet activation or proteolysis of key platelet receptors in patients undergoing liver transplantation. These findings suggest that platelet function may be well preserved during liver transplantation which supports a very restrictive transfusion policy.

Chapter 4 discusses the results of an observational study in which we examined platelet adhesive protein von Willebrand factor (VWF) parameters and ADAMTS13 levels during the course of liver transplantation. We previously demonstrated that highly elevated levels of VWF in patients with cirrhosis compensate for thrombocytopenia and functional platelet defects in these patients (8;9). In the study described in Chapter 4 we have shown that during liver transplantation patients have persistently elevated levels of VWF. Furthermore, an improvement of functional capacity of VWF is shown during the procedure. Concomitantly, these patients acquire a (partial) deficiency of ADAMTS13. Altogether these findings point towards maintenance of a hyperreactive VWF/ADAMTS13 pathway during liver transplantation which compensates for (acquired) platelet defects and reduced platelet counts.

Chapter 5 describes a case-report of transmission of idiopathic thrombocytopenic purpura (ITP) during liver transplantation. A 44-year old male developed a sudden thrombocytopenia after receiving a liver from a donor who died from intracerebral bleeding due to ITP. Despite multiple platelet transfusions, immunoglobulin, and steroid treatment, the severe and life-threatening thrombocytopenia persisted until postoperative day 8 when platelet count slowly started to rise. However, four days later the patient's condition suddenly worsened because of acute portal vein thrombosis, eventually leading to his death. Laboratory studies demonstrated anti-platelet antibodies in serum of both donor and recipient. As other causes for the thrombocytopenia were ruled out, we conclude that the recipient contracted ITP through transmittance of anti-platelet antibody-producing lymphocytes by the liver transplant procedure. The evidence

put forward in this case-report corroborates previously published cases (10;11). Although the condition is likely to be self-limiting, current evidence suggests that patients receiving such a donor liver have difficulties to survive the intervening period. Therefore, we conclude that livers from donors who have died from ITP seem to be dangerous for the recipient, and should not be used, even in era of donor shortage.

Chapter 6 describes a large cohort study in which we assessed the influence of seven prothrombotic gene polymorphisms on the risk of hepatic vessel thrombosis after liver transplantation. In a series of 421 transplant procedures, genomic DNA from both the donor and the recipient was available in 91% of the cases. Results of this study indicate that the presence of Factor V Leiden and the Factor XIII G100T polymorphism in the donor liver and the presence of the methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism in the recipient are associated with an increased risk for hepatic artery thrombosis after liver transplantation. These results indicate that, in addition to technical factors, excessive coagulation activation may contribute to the development of post-transplant thrombosis. However, since the prevalence of these polymorphisms is low, the overall impact on the incidence of HAT is minimal and routine screening for these gene polymorphisms seems not justified.

In **Chapter 7** specific causes of mortality and graft loss in relation to platelet transfusions during liver transplantation are described. The study confirms and extends previous observations regarding the negative effects of platelet transfusions on outcome after liver transplantation (3). Increased postoperative mortality in patients receiving platelets is ascribed to an increased mortality due to acute lung injury or acquired respiratory distress syndrome. Platelet transfusions were not associated with an increased occurrence of graft-related thrombotic complications. Although there is no good alternative therapy for platelet transfusions in the situation of excessive bleeding, it seems advisable to avoid unnecessary prophylactic transfusion of platelets in liver transplant recipients.

In conclusion and discussed in **Chapter 8**, platelet function does not seem to deteriorate during liver transplantation as previously thought. Improvements in surgical and anesthesiological techniques as well as a reduction in the cold ischemia time may explain why platelet function nowadays seems to be preserved. Furthermore, compensatory mechanisms as persistently elevated levels of VWF support platelet function during liver transplantation. Altogether these findings point to a rebalanced primary hemostatic system during liver transplantation. However, the margins are thought to be narrow. This rebalanced hemostatic system might be one of the reasons for the reduction in transfusion requirements of blood products during liver transplantation reported over the last decade. Furthermore, this rebalanced hemostatic system might also be one of the reasons for development of thrombotic events after liver transplantation. Because of narrow margins, the hemostatic system might easily flip over to a hypercoagulable state instead of a hypocoagulable state. This knowledge, combined with the increasing realisation of the detrimental effects of blood product transfusion will lead to a more careful approach of platelet transfusion in the future. Furthermore, future (prospective, controlled, clinical) studies on anticoagulant and antiplatelet therapy to reduce the risk for thrombosis after liver transplantation seem justified.