Hemostasis in Pediatric Liver Transplantation

Werner-Paap, Maureen

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CHAPTER 1

General introduction and outline of this thesis

GENERAL INTRODUCTION

A liver transplantation is a surgical procedure to remove a diseased liver and replace it with a healthy liver (or part of one) from a donor. In 1963 the first liver transplantation was performed by Thomas Starzl and his team in a 3-year old patient with biliary atresia.[1] Unfortunately, the patient died during surgery because of uncontrolled bleeding. In 1967 the first successful liver transplantation was performed (again in a child).[2] Ever since, the field of liver transplantation has been developing greatly. New surgical techniques, intensive perioperative care, introduction of immunosuppressive regimens and close collaboration in organ allocation resulted in improved recipient outcomes. At present, more than 50 years later, liver transplantation is the only curative treatment for both adults and children with end-stage liver disease, and is performed in over 175 centers in Europe.[3]

Although these developments significantly improved outcomes of children with end-stage liver disease, liver transplantation is still an invasive and challenging procedure. At present, two of the main challenges are thrombotic and bleeding complications, which both significantly contribute to morbidity and mortality.[4-6] Incidences of hepatic artery thrombosis of 5-18% and 5-10% for portal vein thrombosis have been reported.[7,8] Bleeding complications occur in 5-20%, warranting proactive hemostatic management.[6] Although several risk factors for both thrombotic and bleeding complications have been identified, it remains unpredictable which individual patient will develop bleeding complications and which patients are prone to thrombotic complications.

Hemostasis, which is the process of blood clot formation at site of blood vessel injury to stop bleeding, plays a key role in the pathogenesis of these complications. The hemostatic process consists of platelet adhesion and aggregation, coagulation and fibrinolysis, and is regulated by the liver. A malfunction in the hemostatic system may lead to bleeding or thrombosis. For a long time, it was thought that patients with end-stage liver disease had a bleeding tendency. However, it now has been firmly established that adults with end-stage liver disease are in a state of 'rebalanced hemostasis'.[9,10] In patients with liver disease concurrent changes in both pro- and antihemostatic pathways occur, which affect platelet aggregation, coagulation, and fibrinolysis, resulting in a new hemostatic balance.[11,12] This rebalanced hemostasis though, is fragile and can easily bend towards thrombosis or bleeding, especially during invasive procedures such as liver transplantation.[13,14]

However, children are not just little adults. Children have different liver disease etiologies, higher incidences of posttransplant thrombosis and a still developing hemostatic system.[15,16] Hemostasis is an evolving age-depending process that starts *in utero* and continues throughout life. Since most of the maturation of the hemostatic system occurs during infancy, hemostasis in children is characterized by age-related changes in the coagulation system, with most hemostatic proteins present in lower levels in children than in adults. More

knowledge of hemostasis in children undergoing liver transplantation is required to safely and efficiently prevent and treat both thrombotic and bleeding complications.

OUTLINE OF THIS THESIS

The **aim of this thesis** is to get a more rational approach to prevention and treatment of thrombotic and bleeding complications in pediatric patients undergoing liver transplantation. Therefore, we identified risk factors for thrombotic and bleeding complications, evaluated the current clinical antithrombotic therapy protocol, assessed hemostatic balance during pediatric liver transplantation and studied effects of therapeutic pro- and antihemostatic therapy agents. Furthermore, the consequences of vascular complications in terms of retransplantation were examined.

In the Netherlands, the first pediatric liver transplantation was performed in 1982. Since then, pediatric liver transplantation is increasingly performed, with currently 25-30 pediatric liver transplantations each year.[17] In the Netherlands, pediatric liver transplantation is centralized in one center, the University Medical Center Groningen. In 2004, living donor liver transplantation was introduced, which presently accounts for half of the pediatric liver transplantations performed in the Netherlands. **Chapter 2** describes a study that evaluates the outcomes of children who underwent a liver transplantation in the Netherlands over the past two decades.

As mentioned, the high incidence of thrombotic complications after pediatric liver transplantation is incompletely understood, but may be related to disease etiology, different plasma levels of hemostatic proteins in children and discrepancy in vessel diameters between donor and recipient, as well as the small diameter of hepatic vessels in children in general.[18,19] To reduce thrombotic complications, a protocol with routine antithrombotic therapy, consisting of unfractionated heparin followed by acetylsalicylic acid, was implemented in clinical practice. In **Chapter 3** we aimed to evaluate incidences of thrombotic and bleeding complications since the implementation of routine antithrombotic therapy and to identify risk factors for these complications.

Since hemostasis plays a key role in the pathogenesis of thrombotic and bleeding complications, especially in patients with end-stage liver disease, we aimed to assess hemostasis in pediatric patients undergoing liver transplantation with a prospective cohort study, as presented in **Chapter 4**. Based on results in adult liver transplantation, we hypothesized that whereas routine laboratory tests demonstrate a hypocoagulable state, more advanced hemostatic tests would indicate intact or hypercoagulable hemostasis.[11,20]

To prevent and treat thrombotic complications, a wide variation of antithrombotic therapy is implemented in pediatric transplant centers worldwide.[21] Yet, an evidence-base for the type of drug, dosing, and timing is lacking. Current anticoagulant therapy protocols and prohemostatic treatment strategies are usually based on experiences in pediatric cardiology or adult liver

transplantation.[22,23] The combination of a rebalanced hemostasis, liver transplantation, and the altered hemostatic state in children compared to adults makes it difficult to translate pro- and anticoagulant treatment regimens to pediatric liver transplantation. In **Chapter 5** we aimed to examine the efficacy of clinically available pro- and anticoagulant drugs in pediatric liver transplantation. *In vitro* effects of different agents were tested in plasma from children undergoing liver transplantation, and compared the effects in children with intact liver function.

After primary liver transplantation, 11 to 15% of children develop graft failure and need to be retransplanted during childhood.[24,26] Importantly, the main cause of graft failure are vascular complications, such as hepatic artery thrombosis. Outcomes after pediatric liver retransplantation are inferior to that of primary liver transplantation.[26,28] In **Chapter 6** we aimed to examine risk factors for pediatric liver retransplantation and develop a risk score to predict patient survival after pediatric liver retransplantation, and with this improve matching donor grafts with recipients.

Apart from thrombotic and bleeding complications, donor organ shortage forms an important challenge in liver transplantation, especially for children, who need a perfect size- appropriate graft.[29] An upcoming strategy in adult liver transplantation to expand the donor pool is the use of preconditioned liver grafts. These preconditioned grafts are optimized and conditioned by using *ex situ* hypothermic machine perfusion, with the supplemental value of providing oxygen to the graft during preservation which ameliorates ischemia-reperfusion injury and offers better preservation of the bile ducts.[30-32] So far, machine perfusion has only been reported in adult liver transplantation. In **Chapter 7** we report the first successful transplantation of a pediatric liver graft after oxygenated hypothermic machine perfusion.

Finally, in **Chapter 8** the results of this thesis are summarized and discussed, followed by future perspectives.

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