Transfusion requirements in orthotopic liver transplantation
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2004

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
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Chapter 7

Summary
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Although blood loss during primary adult liver transplantation has decreased considerably over time, it still has a major impact on mortality and morbidity after liver transplantation. Therefore the studies in this thesis were designed to address the effects and determinants of intraoperative blood loss in order to improve blood loss and subsequently clinical outcome. Chapter 1 gives a general introduction on blood loss in liver transplantation and formulates the questions to be answered by the studies that are described in the ensuing chapters. The number of red blood cell concentrates (RBC) that were transfused to maintain hematocrit values between 0.25 and 0.30 represented blood loss. Measurement of blood loss is considered less accurate than requirements of RBC transfusion, because of dilution of fluid in suction containers by ascites and intraperitoneal hypersecretion.

In chapter 2, a retrospective analysis in 231 consecutive adult patients, who underwent a primary liver transplantation in our centre between January 1994 and January 2002, is described. The incidence of several types of surgical reinterventions performed during the in-hospital stay after orthotopic liver transplantation (OLT) was determined and possible predictive variables were identified. Hundred thirty-nine surgical reinterventions were performed in 79 of 231 patients (34%). Septicemia (44%) and bleeding (27%) were the most frequent indications for surgical reinterventions, followed by biliary reinterventions (10%). Vascular reinterventions, retransplantation and reinterventions for other reasons were performed in 7% each. Of all analyzed variables (gender, age, primary disease, acute liver failure, Child-Pugh classification, Karnofsky score, previous upper right abdominal operations, creatinine clearance, prothrombin time, antithrombin plasma level, platelet count, surgical technique, cold ischemia time, warm ischemia time, functional anhepatic time, anatomical anhepatic time, revascularisation time and year of transplantation), only the number of transfused red blood cell concentrates was identified as independent predictor of surgical reinterventions. Median RBC transfusion requirement was 2.9 L (range, 0–18.8) in the intervention group compared to 1.5 L (range, 0–13.4) in the non-intervention group (P < 0.001). In-hospital mortality was 19% in the reintervention group versus 6% in the non-intervention group (P = 0.003). The mortality rate after the in-hospital stay was the same in both groups (7%). This study revealed intra-operative blood loss as the main determinant of

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early surgical reintervention after liver transplantation and emphasised the need for further and novel attempts to control blood loss during liver transplantation. A second retrospective study was performed to identify variables, which influenced blood loss in 164 consecutive patients, who underwent a primary liver transplantation between 1989 and 1996 (chapter 3). Transfusion of allogeneic and autologous (cell saver) blood was used as an outcome variable instead. Transfusion requirements were associated with age, gender, primary disease, Child-Pugh classification, plasma levels of activated partial thromboplastin time, antithrombin III, urea and serum creatinine, platelet count, year of transplantation, length of cold ischemia time and autologous blood transfusion. Of these variables, Child-Pugh classification ($P = 0.001$), urea plasma level ($P = 0.0007$), year of transplantation ($P = 0.002$), cold ischemia time ($P = 0.01$) and autologous (cell saver) blood transfusion ($P < 0.0001$) were independent predictors of transfusion requirements as demonstrated by multivariate analysis. Mortality within three months after transplantation was markedly related to transfusion requirements ($P < 0.0001$). It was concluded that transfusion requirement in liver transplantation, and hence blood loss, depend on the severity of liver disease, quality of the donor liver (as reflected in a prolonged cold ischemia time), experience of the transplantation team, and autologous blood transfusion by a cell saver. These findings emphasised the need for appropriate hemostatic drug therapy and a critical reappraisal of current transfusion policy to reduce the intraoperative blood loss. The data obtained from this study provided the basis for a pilot study, designed to study recombinant activated factor VII (rFVIIa, NovoSeven®) as a prohemostatic drug in liver transplantation. The efficacy and safety of rFVIIa were assessed in six patients. The results of this dose exploring study are described in chapter 4. Patients were planned to receive a single dose of 80 µg/kg rFVIIa at the start of the operation, and a second dose if necessary to be repeated according to predefined criteria. Packed red blood cell concentrates (RBC), fresh frozen plasma (FFP), and platelet concentrates were administered according to predefined criteria. Perioperative transfusion requirements in study patients were compared with matched controls. Actually, all study patients only received a single dose of rFVIIa. Transfusion requirements (given as median, with range in parentheses) were lower in the study group than in matched controls: 1.5 (0-5) vs. 7 (2-18) units of allogeneic RBC ($P = 0.006$), 0 (0-2) vs. 3.5
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(0-23) units of autologous RBC (P = 0.043), total amount of RBC 3 (0-5) vs. 9 (4-40) units (P = 0.002). Transfused FFP amounted 1 (0-7) vs. 8 (2-35) units (P = 0.011). Blood loss was 3.5 L (1.4-5.3) vs. 9.8 (3.7-35.0) (P = 0.004). One study patient developed a hepatic artery thrombosis at day 1 postoperatively. It was concluded that a single dose of 80 μg/kg rFVIIa significantly reduced transfusion requirements during liver transplantation, and that larger sized studies should establish the optimally effective and safe dose of rFVIIa in liver transplantation. In chapter 5 the influence of rFVIIa on coagulation and fibrinolysis during liver transplantation in the six afore mentioned patients who had received a single dose of 80 μg/kg rFVIIa was assessed. Plasma levels of coagulation factors, and parameters of thrombin generation and fibrinolysis, respectively, were measured. Controls were ten liver transplant patients not treated with rFVIIa. This study revealed that coagulation factor plasma levels did not differ between study patients and controls. Thrombin generation did not rise after rFVIIa administration, but sharply increased after reperfusion in study patients as compared with controls. No difference in fibrinolysis was seen between study patients and controls. The administration of rFVIIa apparently enhances thrombin generation in a localised and time limited matter, without causing systemic coagulation.

In chapter 6 the effects of rFVIIa on conventional coagulation variables, as compared with thromboelastography (TEG) were assessed. In the six study patients, the prothrombin time (PT), the activated partial thromboplastin time (APTT), and TEG variables i.e. reaction time (r), kinetic time (k), α angle (α), and maximal amplitude (MA), were recorded before and after the administration of a single dose of 80 μg/kg rFVIIa. Study patients were compared with six controls who had not received rFVIIa. In contrast with controls, a significant shortening of the PT (P = 0.028) and APTT (P = 0.028), r (P = 0.046) and k (P = 0.043) values, and a significant incline of the α angle (P = 0.028) were noticed after the administration of rFVIIa. MA did not increase significantly (P = 0.075). These results indicate that rFVIIa rapidly improved coagulation variables in liver transplant patients. Apparently, rFVIIa not only influences the speed of clot formation, but also the physical properties of the clot, which can only be detected by TEG.
Chapter 8

Conclusions and recommendations