Transfusion requirements in orthotopic liver transplantation

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Chapter 1

Introduction

The first human orthotopic liver transplantation was performed in March 1963 by Starzl [1]. Unfortunately, as Starzl stated, "He bled to death as we worked desperately to stop the haemorrhage" [2]. It was also reported by this pioneer that in the early years of transplantation, "It was clear that however seriously disturbed clotting was at the outset, it usually became even worse once the liver transplantation was started" [2]. It is no wonder that at that time the success rate of this extensive procedure was low because of frequent perioperative exsanquination [3,4,5]. Nowadays, 40 years after its start as an experimental procedure, liver transplantation is the treatment of choice in patients with acute or chronic end stage liver disease, irresectable primary liver tumors, as well as a variety of metabolic disorders [6]. Despite improvements during the last decades in surgical technique, anesthesiologic management and organ preservation [7,8], intraoperative blood loss and the subsequent transfusion of large amounts of blood products still pose a major concern [9]. The liver plays a central role in hemostasis. Hemostasis is the result of a complex process, including pro- and anticoagulant proteins, pro- and antifibrinolytic proteins, and platelet activators and inhibitors (Figure 1). The liver exclusively or mainly produces most of the proteins involved in coagulation and fibrinolysis. Moreover, this organ is responsible for the clearance of these proteins after they have been activated. Under normal circumstances balanced interactions of pro- and anticoagulant proteins, pro- and antifibrinolytic proteins, and platelet activation and inhibition maintain the integrity of the vessel wall, as well as vessel patency. In patients with chronic end-stage liver disease, impaired synthesis results in decreased plasma levels of most mentioned proteins. Such an imbalance may result in a hypocoagulable state if a deficiency of pro-coagulant proteins predominates, or in a hypercoagulable state due to a deficiency of anticoagulant proteins, or a reduced clearance of activated procoagulant proteins by the liver. A hyperfibrinolytic state may occur if there is a deficiency of anti-fibrinolytic proteins, or increased release of pro-fibrinolytic proteins or decreased clearance of pro-fibrinolytic proteins.
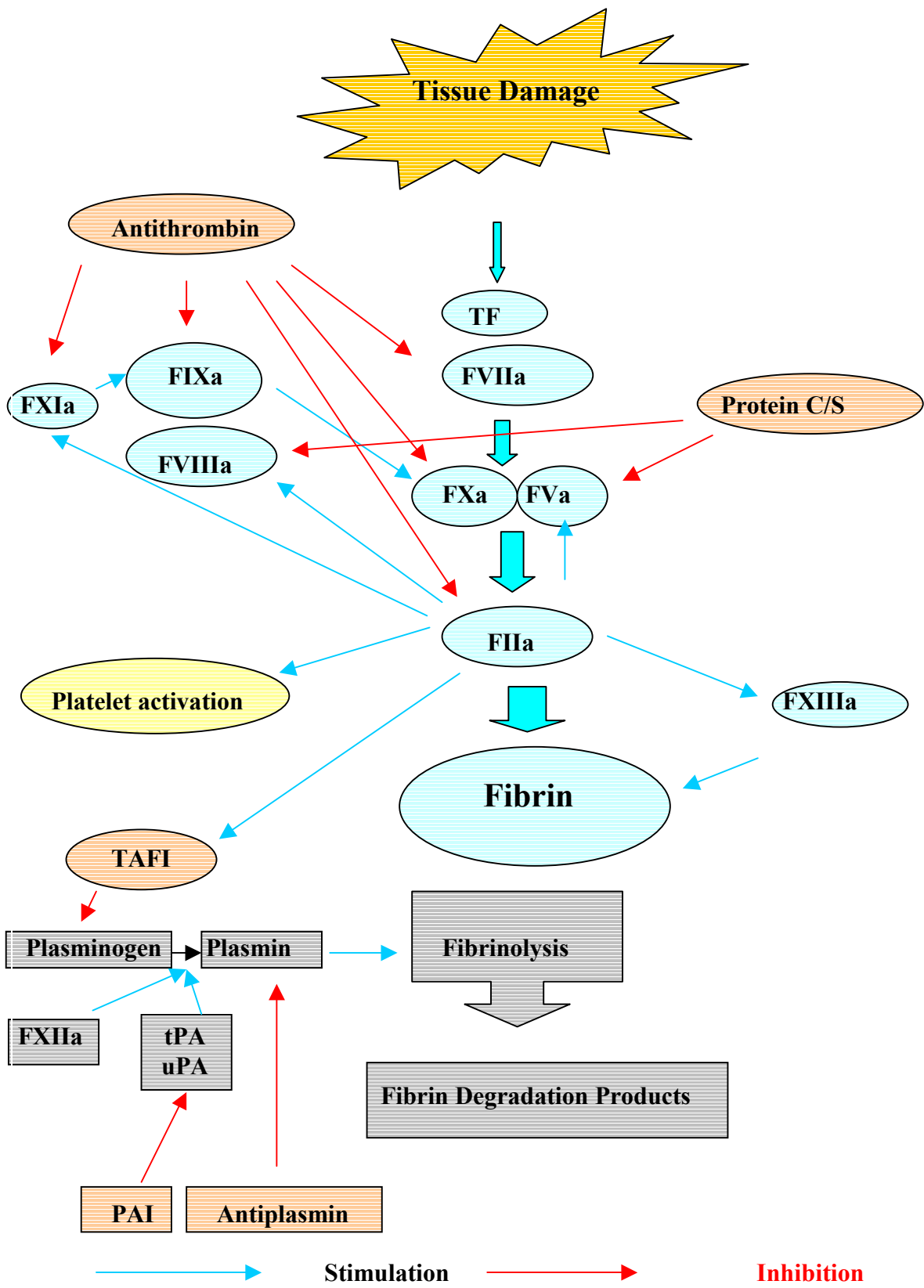
Figure 1 *Mechanism of coagulation and fibrinolysis*

A hypofibrinolytic state may occur if the fibrinolytic potency is decreased by a deficiency of pro-fibrinolytic proteins (Table 1). Chronic disseminated intravascular coagulation, due to insufficient inhibition of activated coagulation, may worsen the imbalance by consumption of procoagulant proteins and platelets, and reactive hyperfibrinolysis. Increased levels of fibrin degradation products, secondary to hyperfibrinolysis and a decline of their clearance, cause platelet inhibition. Thrombocytopenia, a common finding in patients with liver cirrhoses, portal hypertension and hypersplenism is explained by pooling of platelets in the enlarged spleen and suppressed thrombocytopoiesis. Overall, in cirrhotic patients these changes in the hemostatic mechanism usually result in hypocoagulation, and hence an increased risk of haemorrhage. However, a different situation can occur in patients with primary biliary cirrhosis and primary sclerosing cholangitis. These patients have been associated with hypercoagulabilty, possibly due to platelet activation [10]. During liver transplantation, the patient swings between the risks of bleeding and thrombosis, depending on the changes in the hemostatic balance, that are typical for the different phases and circumstances of liver transplantation. Besides hemostatic abnormalities inherent to liver disease, the surgical procedure itself enhances blood loss. Often, the native liver is caught in adhesions. Portal hypertension leads to numerous collaterals especially in these adhesions, which, together with increased capillary fragility, can make the maintenance of surgical hemostasis during explantation of the native liver cumbersome [9].

Blood loss during liver transplantation has important consequences for postoperative morbidity and mortality. It has been demonstrated that patients with high transfusion requirements stay longer in the intensive care, have more infections and a higher rate of graft loss, and consequently have a higher mortality rate [11,12,13,14,15]. Graft and patient's survival has shown to be impaired in patients who received more than 10 units of red blood cell concentrates [11]. Therefore, attempts by surgeons and anaesthetists have been made to reduce intraoperative blood loss.

Surgeons over the years have adapted their explantation technique of the native liver and implantation technique of the graft. It took some time before it was recognised that meticulous hemostasis during the explantation phase was of paramount importance. The introduction of the veno-venous bypass by Shaw et al. [13], and later modified by our group [16], further reduced the intraoperative transfusion requirements. This bypass regulates

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outflow through a cannula placed in the femoral vein, with a second cannula in the portal or inferior mesenteric vein. Blood is returned via the axillary or internal jugular vein via a biopump. The use of heparin-bonded cannulas and a (non-occlusive) biopump allowed application of the bypass without need for systemic heparinization. This technique enables decompression of the portal, lower caval and renal venous systems and subsequently facilitates control of bleeding. Also the cardiac output is maintained, and the splanchnic, renal and coronary blood flows are preserved. However, such a bypass requires expensive disposables, extra personnel and prolonges the operating time. Also the patient needs two extra incisions: in the groin and axilla. But the most serious hazard of a bypass is embolization of air or a thrombus. This may occur when the portal cannula is dislodged, or when thrombus originates in the bypass tubing during a period of low flow or occlusion.

Table 1 *Hemostatic abnormalities in liver disease*

Hypocoagulability

Deficiency of coagulation factors by impaired synthesis (excepted factor VIII and von Willebrand factor)

Synthesis of abnormal clotting proteins (dysfibrinogenemia)

Impaired clearance of activated coagulation factors and degradated fibrin

Vitamin K deficiency

Hypercoagulability

Decreased levels of antithrombin, protein C or protein S by impaired synthesis

Enhanced fibrinolytic activity

Increased levels of circulating t-PA by impaired hepatic clearance

Reduced synthesis of fibrinolytic inhibitors (α2- antiplasmin,plasminogen activator type 1)

Quantitative and qualitative platelet defects

Splenic pooling of platelets

Defected bone marrow production of platelets

Disturbed platelet-vessel wall interaction

Inhibition of GP IIb/IIIa by increased levels of fibrin degradation products

Degraded platelet receptors by increase in plasmin levels

Disseminated intravascular coagulation

Consumption of coagulation factors and platelets

Hyperfibrino(geno)lysis

Impaired platelet function due to fibrin degradation products, secondary to hyperfibrinolysis

Not only the explantation technique has been adapted, but also the implantation technique changed over time to decrease peroperative blood loss. In 1989 a new graft implantation technique was introduced by Tzakis et al. [17]. With this technique the inferior caval vein of the recipient is preserved and the upper caval cuff of the donor liver is anastomosed either to a common orifice in the hepatic veins or to a longitudinal incision in the inferior caval vein. With this so-called piggyback technique transfusion requirements became even more reduced [15]. As a consequence of this new technique the veno-venous bypass became redundant. Also the costs of the piggyback procedure are lower compared to the conventional technique. New surgical devices like argon beam coagulator became available and have further contributed to a reduction of transfusion requirements during liver surgery [12]. Anesthesiological measures to reduce intraoperative blood loss are focused on the correction of coagulation abnormalities during transplantation, and the maintenance of a low central venous pressure. It became apparent that massive bleeding is associated with severe problems, like acute hypovolemia, citrate intoxication, low levels of ionized calcium, hyperkalaemia, acidosis, and hypothermia. Coagulation abnormalities are corrected by the administration of blood components, such as fresh frozen plasma, prothrombin complex concentrates, cryoprecipitate, fibrinogen concentrates and platelet concentrates. Plasma constituents are usually administered to maintain prothrombin times below 1.5 times the upper limit of the normal range, and platelet concentrates to keep platelet counts above 50 x 10^9 /L [18]. Antithrombin concentrates have been used intraoperatively to increase the inhibitory potential against thrombin formation, but the results of prospective, randomised, controlled studies were not conclusive [19,20]. More recently, pharmacological agents directed to the inhibition of hyperfibrinolysis, that is most pronounced early after reperfusion of the graft, have been introduced [7,21]. Antifibrinolytic drugs, like epsilon aminocaproic acid [22], tranexamic acid [23], and aprotinin [24] are applied to reduce the intraoperative blood loss during liver transplantation. Recently, two placebo-controlled studies showed a reduction in transfusion requirements during liver transplantation by 30 to 40% using aprotinin [25,26].

Hemostatic abnormalities may also arise from hypothermia and metabolic acidosis. Patients often suffer from hypothermia during long and extensive operations, especially when large volumes are transfused without precautions. Large uncovered body surface areas, evaporation and convective cooling cause hypothermia [27]. Biologic enzyme systems act optimally

within a very narrow temperature range [28,29]. This is reflected in the reported linear correlation between a decreased body core temperature and prolonged PT and aPTT values [28]. Active warming of the patient by a warm touch [27] and administering all fluids at a temperature of 39^0 C [30] showed to be effective. Special bags to collect fluids during the operation avoid the patient's contact with fluids, and so prevent cooling of the patient by evaporation. The effects of metabolic acidosis on hemostasis have not yet been elucidated, but probably include platelet inhibition [29].

Monitoring of hemostasis during liver transplantation is an important issue, considering the complexity of hemostatic abnormalities in these patients. Moreover, it is important to assess the effects of treatment of these hemostatic abnormalities. Standard coagulation tests, such as activated partial thromboplastin time, prothrombin time, and measurement of plasma fibrinogen levels are performed on plasma at 37^0C. These tests neglect the in vivo role of temperature, and interactions with platelets and red blood cells in clot formation. They only enable to screen for deficiencies of one or more coagulation factors. Simple and reliable tests to quantify changes in fibrinolysis are not available. Tests of fibrin degradation products, like D-dimers, may identify excessive hyperfibrinolysis, but are less valuable to assess the clinical effects of antifibrinolytic drugs. Measurement of the euglobulin clot lysis time is time consuming and provides information about the fibrinolytic potential, but excludes the effect of fibrinolytic inhibitors. Several authors failed to find any correlation between the results of these screening tests of hemostasis before operation and the transfusion requirements during liver transplantation [11,31,32]. Also the results of intraoperative standard coagulation test did not correlate with intraoperative transfusion requirements [32,33,34]. Hence, there is still a ongoing debate about the most appropriate tests and the frequency of testing [35].

The central venous pressure (CVP) is directly related to the pressure in the hepatic veins. A high CVP, resulting in distending central veins, augmenting the intraoperative blood loss has been proven during liver resection [36,37]. The same effects are present during explantation of the native liver for transplantation. The venovenous bypass technique requires euvolemia or, in most cases, hypervolemia of the patient, causing a high CVP. When surgeons changed their explantation technique from the venovenous bypass to the piggyback procedure, the intravenous fluid needs of the patient dropped, resulting in a low CVP during the explantation of the native liver. The anesthetic technique, designed to maintain a CVP to less than 5 cm H_2O, helps to minimise blood loss during the explantation of the liver.

Attention to the above-mentioned surgical and anesthesiological measures has resulted in a reduction of intraoperative blood transfusion requirements in our program. Figure 2 shows the required transfusions of red blood cell concentrates (RBC) over the years in primary adult liver transplant patients in our institute. Median transfusion requirements decreased from 12.500 ml in 1979 to 500 ml in 2002, a decline that has to be ascribed mainly to improved surgical techniques and anesthesiological management.
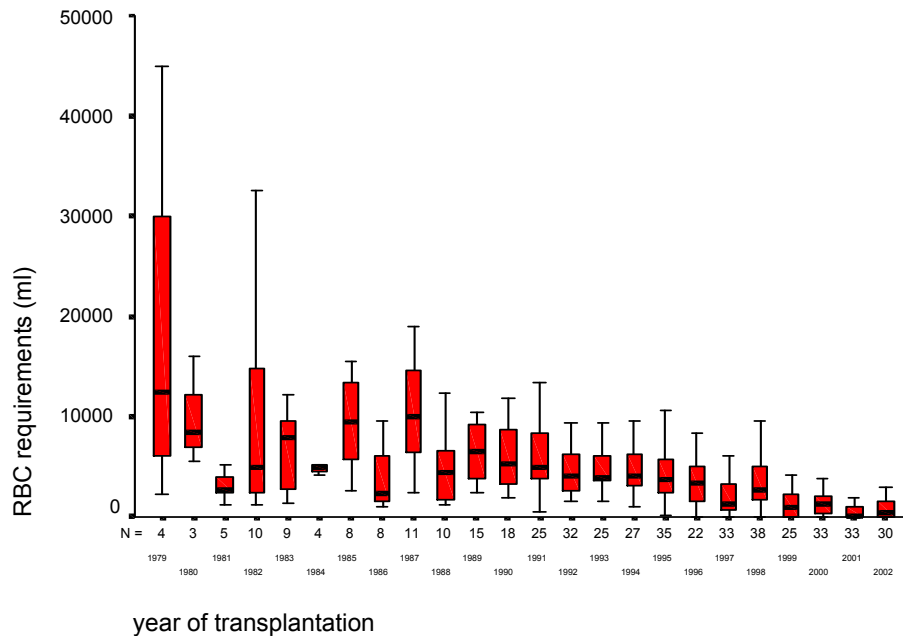
Figure 2. *Intraoperative red blood cell transfusion requirements (in ml) during primary adult orthotopic liver transplantation at the Groningen University Hospital from the start of the program in 1979 until 2003.*

Horizontal lines in the boxes represent median values, boxes represent 25th and 75th percentiles. Vertical lines represent maximal and minimal values. N represents the annual number of transplantations. RBC, red blood cell concentrates

Despite the current low transfusion needs in our and other experienced centres, there is still a significant negative correlation between transfusion requirements and mortality and morbidity [38,39,40]. The research presented in this thesis was performed to find a rational approach to further decrease intraoperative blood loss and consequently to improve clinical outcome.

Outline of the thesis

In chapter 2 a study is presented which was performed to assess the relationship between RBC transfusion requirements (i.e. blood loss) and surgical reinterventions, to assess the relation between peroperative blood loss and clinical outcome after liver transplantation. In chapter 3 a retrospective study is described that was conducted to identify predictors of blood loss during liver transplantation. Also the putative benefits of cell saving were evaluated. The data provided by this study were used to design a dose finding pilot study of recombinant activated factor VII in liver transplantation. Recombinant factor VIIa (rFVIIa, NovoSeven [®], Novo Nordisk, Copenhagen, Denmark), effective in a variety of hemostatic disorders, was not evaluated yet in liver transplantation. Its efficacy and safety in liver transplantation are reported in chapter 4. The changes in the hemostatic mechanism induced by this drug are described in chapter 5. An evaluation of thromboelastography as a technique to monitor actual hemostasis in patients undergoing liver transplantation and receiving rFVIIa during the procedure is presented in chapter 6. Finally, the findings of these studies are summarised in chapter 7 and conclusions and recommendations are formulated in chapter 8.

Aim of the thesis

The aim of the thesis was to:

1) analyse the impact of transfusion requirements during primary adult liver transplantation on clinical outcome,

2) identify predictors of transfusion requirements in primary adult liver transplantation,

3) assess the efficacy and safety of pharmacological intervention with rFVIIa in liver transplantation,

4) analyse the changes in hemostasis induced by rFVIIa during liver transplantation,

5) evaluate thromboelastography as a device to monitor actual hemostasis in patients receiving rFVIIa during liver transplantation.

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