Impact of hemostasis and blood loss on outcome after liver surgery

de Boer, Marieke T.

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2015

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Download date: 08-12-2018
Minimizing blood loss in liver transplantation: progress through research and evolution of techniques

Marieke T. de Boer
I. Quintus Molenaar
Herman G.D. Hendriks
Maarten J.H. Slooff
Robert J. Porte

ABSTRACT
Blood loss during liver transplantation has long been recognized as an important cause of morbidity and, especially in the early days, also mortality. It is well known that blood transfusions are associated with an increased risk of postoperative complications, such as infections, pulmonary complications, protracted recovery, and a higher rate of reoperations. Many studies have been performed during the past decades to elucidate the mechanisms of increased blood loss in liver transplantation. In the late 1980s, primary hyperfibrinolysis was identified as an important mechanism of bleeding during liver transplantation. This has provided the scientific basis for the use of antifibrinolytic drugs in liver transplant recipients. Several randomized, controlled studies have shown the efficacy of these compounds in reducing blood loss and transfusion requirements during liver transplantation. In addition, increasing experience and improvements in surgical technique, anesthesiological care and better graft preservation methods have contributed to a steady decrease in blood transfusion requirements in most liver transplant programs. Several centers are now reporting liver transplantation without any need for blood transfusion in up to 30% of their patients. Despite these improvements, most patients undergoing liver transplantation still require blood transfusions that have a negative impact on outcome, emphasizing the need for further attempts to control blood loss by surgeons and anesthesiologists. This paper provides an overview of the clinical and research developments, which have contributed to a reduction in blood loss and transfusion requirements, resulting in an important reduction in morbidity and mortality after liver transplantation during the last two decades.
INTRODUCTION

Liver transplantation is an accepted treatment for end-stage chronic liver disease, fulminant hepatic failure, irresectable primary liver tumors and various metabolic disorders. One-year patient survival after liver transplantation is about 80-90% and long-term survival is around 70%. Currently, more than 10,000 liver transplantations are performed each year in Europe and North America. The first human liver transplantation was reported by Starzl et al. in 1963. Unfortunately, this first patient died of exsanguination during the procedure, exemplifying what would become one of the most important barriers in liver transplantation in the following years. Many hurdles towards successful liver transplantation have been overcome since then and the number of liver transplantations has increased progressively during the last four decades. The introduction of cyclosporine in the early 1980s was a major step forward in the reduction of acute rejection as a cause of graft loss. The development of the University of Wisconsin preservation solution in the late 1980s reduced graft preservation injury and allowed longer cold ischemia times. In parallel with these innovations, surgical techniques have evolved, resulting in a more standardized and less blood consuming procedure. Liver transplantation has changed from an emergency procedure with an unpredictable outcome, to a semi-elective, better controlled procedure, with a high likelihood of success.

Until the mid 1980s, liver transplantation was accompanied by high morbidity and mortality rates, frequently related to high intraoperative blood loss and transfusion requirements. During the past 15 years, a steady decrease in blood loss and transfusion requirements has been observed in most experienced centers. (Figure 1) The explanation for this is multifactorial. Extensive research

Figure 1. Red blood cell transfusion requirement in adult patients undergoing a first orthotopic liver transplantation at the University Medical Center Groningen between 1989 and 2003. Data presented as box plots, representing median, interquartile range, and 5–95% range (updated from Porte et al.)
on perioperative changes in coagulation and fibrinolysis has improved the understanding of the hemostatic disorders that are associated with liver transplantation. Based on this, new pharmacological strategies have been developed to correct hemostatic abnormalities and reduce blood loss. In addition, improvements in surgical technique, anesthesiological care, as well as organ preservation have contributed to a steady reduction of transfusion requirements. The number of patients without any need for blood transfusion has increased in recent years. (Figure 2) This paper provides an overview of the clinical and research developments in the field of hemostasis, as well as surgical technique and anesthesiological care, which have contributed to the impressive reduction in blood loss and transfusion requirements, contributing to an important reduction in morbidity and mortality after liver transplantation during the last two decades.

Figure 2. Percentage of adult patients, undergoing a first orthotopic liver transplantation at the University Medical Center Groningen in the period 1992–2003, who did not require intraoperative, allogenic red blood cell transfusion (updated from Porte et al.).

Impact of blood loss and transfusion requirements on outcome
It is well known that blood transfusions have an immunosuppressive effect and are associated with the induction of several complications, such as pulmonary edema. This may account for the negative correlation between the amount of intraoperative blood transfusion and postoperative outcome, as has been described by several groups. Even today, in centers with median red blood cell transfusion requirements of 2-3 units in adult patients, a significant correlation between intraoperative blood transfusion requirement and postoperative infection rate and morbidity can still be found. In parallel with this, we have observed an association between long-term patient survival rates and the number of intraoperative red blood cell transfusions during adult
liver transplantation. Also in pediatric patients, increased blood loss is a significant independent negative predictor of long-term actual patient survival,15 probably caused by a higher incidence of reinterventions and septic complications in this group of patients. In a recent analysis of 231 consecutive adult liver transplants transplanted in Groningen, intraoperative blood loss was found to be the main determinant of early surgical reinterventions after liver transplantation. Independent risk factors for blood transfusion, identified by multivariate analyses, are kidney function, preoperative hematocrit, preoperative medical condition (Child-Pugh classification, United Network of Organ Sharing Classification), year of transplantation, cold ischemia time of the donor liver, and variables related to the surgical technique. In addition to these factors, specific pre- and intraoperative disturbances in the hemostatic system may occur in liver transplant recipients, contributing to a high bleeding tendency in these patients.

Hemostatic disorders in liver transplantation

Extensive research in the field of hemostasis has led to a marked development of this part of medicine during the last 20 years. Specific hemostatic disorders responsible for non-surgical blood loss during liver transplantation, like primary hyperfibrinolysis, have been identified. Hemostatic disorders in liver transplant patients are primarily caused by the underlying liver disease. During the transplant procedure, depending on the stage of operation, these preexisting disorders may worsen and new hemostatic disorders are superimposed.

Preoperative hemostatic dysfunction

The liver plays a central role in the hemostatic system and liver failure may lead to dysfunction of several components of normal hemostasis. The liver produces and regulates several proteins of the coagulation and fibrinolysis cascades. In the normal situation these two proteolytic cascades are in a delicate balance. Activation of the coagulation system is evoked by vessel injury, which leads to aggregation and activation of platelets by components of the exposed subendothelium and subsequent formation of a primary hemostatic platelet plug. This plug is subsequently stabilized by fibrin formation. Fibrinolysis, a more slow-acting process, is responsible for removal of fibrin clots once the integrity of the vessel wall has been restored. The reticuloendothelial system

<table>
<thead>
<tr>
<th>Table 1. Processes contributing to hemostatic disorders in liver disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced synthesis of coagulation and fibrinolysis factors and their inhibitors</td>
</tr>
<tr>
<td>Presence of qualitative abnormal coagulation factors</td>
</tr>
<tr>
<td>Thrombocytopenia and platelet dysfunction</td>
</tr>
<tr>
<td>Increased fibrinolytic activity</td>
</tr>
<tr>
<td>Influence of red cells and hemolysis</td>
</tr>
<tr>
<td>Loss of hemostatic factors in enlarged extravascular space</td>
</tr>
<tr>
<td>Portal hypertension with reduced hepatic perfusion, shunt circulation, and sequestration of platelets in the enlarged spleen</td>
</tr>
</tbody>
</table>
of the liver contributes to the clearance of hemostasis factors and their degradation products. In chronic liver disease, dysfunctioning synthesis and clearance of hemostatic factors can lead to poor hemostasis.\textsuperscript{6,20} Consequently, intraoperative changes in hemostasis and blood loss during liver transplantation are strongly related to the severity of the liver disease.\textsuperscript{6,19} In addition to this, hypersplenism secondary to portal hypertension is responsible for the decreased number of circulating platelets, contributing to the hemostatic dysfunction.

\textit{Intraoperative hemostatic dysfunction}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{hemostatic_disease_diagram.png}
\caption{Schematic presentation of the balance between coagulation and fibrinolysis, and the levels at which antifibrinolytic drugs interfere with the fibrinolytic system (----- = activation, - - - = inhibition). EACA = \(\varepsilon\)-Aminocaproic acid; TAC = tranexamic acid; KIU = kallikrein inhibiting units; HMWK = high-molecular-weight kininogen; t-PA = tissue plasminogen activator; FDPs = fibrin degradation products.}
\end{figure}

\textit{Hyperfibrinolysis.} When discussing changes in hemostasis during liver transplantation, it is important to keep the three stages of the surgical procedure in mind. The first stage is the preanhepatic stage, during which the host liver is removed, ending with the occlusion of the native liver blood flow. Blood loss during this stage merely reflects the preoperative condition depending on the etiology and severity of liver disease and the experience of the surgeon.\textsuperscript{19,21} Serious changes in coagulation and fibrinolytic activity are usually not found in this stage of the operation.\textsuperscript{19,21} The second stage is the anhepatic stage, which begins with the vascular exclusion of the native liver and continues until the donor liver is reperfused. In this stage, hepatic synthesis and clearance are absent. In this stage there are not many surgical dissections and the major abdominal vessels are clamped off. Therefore, blood loss during this stage of the operation originates mainly from hemostatic defects. Diffuse blood loss may occur in previously dry surgical fields. Hyperfibrinolysis, the most striking hemostatic disorder in liver transplantation, may develop during this stage.\textsuperscript{19,22} Hyperfibrinolysis is caused by a rise in plasma levels of tissue-plasminogen activator (t-PA), the most important endogenous
activator of plasminogen. Plasminogen activators stimulate the conversion of plasminogen into plasmin, which is the active enzyme that degrades fibrin into fibrin degradation products. Plasma t-PA activity increases rapidly during the anhepatic and early post-reperfusion stage, the third stage of the operation. The increase in t-PA is believed to be caused by a lack of hepatic clearance during the anhepatic period and the release of t-PA from the ischemically injured endothelium of the donor liver at the time of reperfusion. Elevation of t-PA results in the consumption of the naturally occurring inhibitor, plasminogen activator inhibitor-1, causing imbalance in the fibrinolysis cascade and premature breakdown of hemostatic clots. Usually, t-PA activity normalizes during the late post-reperfusion stage, which has been explained by the restoration of the normal hepatic clearance of t-PA after the implantation of a viable donor liver. Increase of the inhibitor, plasminogen activator inhibitor-1, towards the end of the operation also contributes to a decline in t-PA activity. Although it is not fully understood why some patients develop high t-PA plasma levels, whereas others do not, hyperfibrinolysis in liver transplant recipients is considered to be of primary origin and not secondary to intravascular thrombosis. This knowledge has provided the basis for interventional studies using antifibrinolytic drugs (see below).

**Thrombocytopenia and platelet dysfunction**

Platelet count often decreases during liver transplantation, especially after graft recirculation, contributing to an increased bleeding tendency. Postoperatively, platelet count may continue to decline further, usually reaching a nadir on postoperative day 2 or 3, after which it slowly recovers.

---

---
towards normal values. In addition, changes in platelet function, as reflected by a transient prolongation of bleeding time and abnormal platelet function studies, have been found in both clinical and experimental studies. Experimental studies have suggested a role for the transplanted liver in the origin of thrombocytopenia. Platelets sequestrate in the sinusoids of the donor liver upon reperfusion. Simultaneous measurements of platelet count in the arterial inflow and venous outflow showed a reduction of 55% in the platelet count in reperfused grafts. The degree of platelet loss has been shown to be related to the severity of ischemia/reperfusion injury of the liver. Intrahepatic platelet sequestration in the sinusoids, local thrombin formation on the damaged graft endothelium, platelet extravasation in the spaces of Disse, and increased platelet phagocytosis by Kupffer cells have all been hypothesized as an explanation for thrombocytopenia. Electron microscopic studies, however, have showed most platelets lying free in the sinusoids, although many of them having lost their granules. Platelet aggregates, as a result of coagulation, are rarely seen. Therefore, the sequestration of platelets inside the reperfused liver is most likely independent from the activation of coagulation. Experimental studies using isolated perfused rat livers have demonstrated that platelets stick to the sinusoidal endothelial cells and contribute to ischemia/reperfusion injury of the liver by the induction of apoptotic cell death of endothelial cells. Adhesion molecules of the selectin family play a critical role in this interaction between platelets and endothelial cells inside the liver. Based on these observations, it is currently advised to avoid platelet transfusions in liver transplant recipients, especially after reperfusion of the graft.

Heparin(-like) activity
A heparin-like effect can be seen after graft reperfusion and may contribute to coagulopathy. This effect has been explained by the release of heparin from the donor liver after heparinization of the donor, or by release of endogenous heparin-like substances from the damaged ischemic graft endothelium. This effect is generally short-lasting. However, some patients may have a greater sensitivity to heparin and may not clear these substances adequately, supporting the use of protamine sulfate when heparin activity is documented in the setting of increased blood loss.

Humoral and metabolic factors
In general, metabolic acidosis, reduced cardiovascular performance, low ionized plasma calcium and hypothermia can adversely affect the hemostatic system. All these changes can be observed during liver transplantation and may play a role in the appearance of hemostatic disorders after graft recirculation. Coinciding with the recovery of the above metabolic abnormalities about 30 min after graft recirculation, improved blood coagulability has been observed by thromboelastography, despite the lack of significant changes in coagulation factors.
Evolution of surgical techniques to minimize blood loss

Liver transplantation is a major surgical procedure and it is beyond doubt that surgical skills and experience have an important impact on intraoperative blood loss during this procedure. Changes in surgical technique have contributed to a reduction in blood loss during liver transplantation. Venovenous bypass, introduced in the 1980s, allows decompression of the splanchnic and retroperitoneal circulations, avoiding major hemodynamic changes during the anhepatic phase of a ‘classical’ liver transplantation.33 Although never formally proven by a randomized controlled trial, it has been suggested that venovenous bypass also results in a reduction of intraoperative blood loss.33 Another important step forward has been the introduction of the so-called ‘piggyback’ technique.34,35 In contrast with the ‘classical’ technique of liver transplantation, in the piggyback technique the retrohepatic inferior vena cava (IVC) is not removed together with the native liver. The retrohepatic IVC of the donor liver is subsequently anastomosed in an end-to-end fashion to the cuffs of the native hepatic veins or directly to the recipient IVC using a side-to-side or end-to-side technique. (Figure 5) A major advantage of the piggyback technique is the avoidance of dissection of the retroperitoneum in patients with portal hypertension and multiple venous collaterals in this area. Moreover, the warm ischemia time during implantation of the graft is shorter in the ‘piggyback’ technique since only one cavo-caval anastomosis has to be made, compared to the two end-to-end anastomoses of the IVC in the ‘classical’ technique.36 In a recent comparison of the two techniques, we demonstrated significantly lower blood transfusion requirements in patients in

Figure 5. Cavo-cavostomy viewed from the left side of the patient in the ‘piggyback’ technique. The retrohepatic inferior vena cava of the donor liver is anastomosed to the recipient inferior vena cava using a side-to-side or end-to-side technique (drawing kindly provided by Balázs Nemes).
whom the ‘piggyback’ technique was used, compared with patients transplanted using the ‘classical’ technique. Similar observations have been made by other groups.

**Evolution of anesthesiological management to improve hemostasis**

Anesthesiological measures to reduce intraoperative blood loss focus on the monitoring and correction of coagulation abnormalities. Massive bleeding is associated with severe problems, such as citrate intoxication, low levels of ionized calcium, hyperkalemia, metabolic acidosis, and hypothermia. Mostly, coagulation abnormalities are corrected by the administration of blood components, such as fresh-frozen plasma, or fibrinogen concentrate and platelet concentrates. In addition, pharmacological prohemostatic agents are used successfully in patients undergoing liver transplantation, as will be discussed below. Coagulation abnormalities may become aggravated by hypothermia or metabolic acidosis. Hypothermia occurs during long operations, especially when large volumes are transfused without precautions. Decreased body core temperature is linearly correlated with prolonged clotting times. Administering fluids at a temperature of 39°C and active warming of the patient by heating blankets have shown to be effective measures to avoid hypothermia. The mechanisms by which metabolic acidosis affects hemostasis are not fully understood, but probably include inhibition of platelet function.

Adequate monitoring of hemostasis is essential to detect coagulation abnormalities in time and to evaluate the effects of therapy. Standard coagulation tests, such as activated partial thromboplastin time, prothrombin time, and measurement of plasma fibrinogen levels only enable to screen for deficiencies of one or more coagulation factors. These tests are performed in plasma samples at 37°C, neglecting the in vivo role of temperature and interactions with platelets and red blood cells in clot formation. Results of these screening tests before and during operation have not shown a very good correlation with the amount of blood loss during liver transplantation. In addition, simple and reliable laboratory tests to quantify changes in fibrinolysis are not available. Therefore, the use of thrombelastography has been advocated as a tool to monitor hemostasis during liver transplantation. Thrombelastography whole blood is used. It provides a dynamic representation of various aspects of clot formation as well as fibrinolysis. Thrombelastography can be used as a point-of-care diagnostic test and results can usually be obtained within 30 min. Kang et al. were amongst the first to use thrombelastography as a guide to blood product replacement and prohemostatic drug therapy during liver transplantation.

With the wider application of the ‘piggyback’ technique, measures to maintain a low central venous pressure (CVP) have become possible. The CVP is directly related to the hepatic vein pressure. During liver resections there is an almost linear correlation between intraoperative blood loss and the height of the CVP. Maintaining the CVP below 5 cm H₂O, by reducing intravenous fluids, may therefore help to minimize blood loss during explantation of the liver. When the ‘classical’ technique is used, patients usually do not tolerate a low CVP when the IVC is clamped during the anhepatic phase. However, with preservation of the retrohepatic IVC in the, nowadays more frequently used,
'piggyback' technique the retrohepatic IVC can be clamped only partially with a side-biting clamp. (Figure 5)

Blood loss during OLT can be corrected by allogeneic or autologous (cell saver) transfusion. Although autotransfusion of blood is an attractive alternative to allogeneic blood transfusions, we do not routinely use the cell saver in our liver transplant patients. The low amounts of blood loss encountered in recent years did no longer allow a cost-effective use of the cell saver. Also, in a retrospective study, we unexpectedly observed higher blood loss in patients when using the cell saver. A possible explanation for this is that released fibrinolytic compounds from blood cells in the collected blood are not washed out adequately by the cell saver. However, the exact mechanisms remain unclear and further research in this area is warranted.

Pharmacological strategies to reduce blood loss

Although the cause of increased blood loss during liver transplantation is multifactorial, primary hyperfibrinolysis has been identified as an important component of the hemostatic dysfunction during this procedure. This has provided a scientific basis for the use of antifibrinolytic drugs, in an attempt to restore the balance between coagulation and fibrinolysis and to reduce blood loss.

Aprotinin

Aprotinin is a low-molecular-weight serine-protease inhibitor with potent antifibrinolytic activity. It is known as an inhibitor of several naturally occurring serine-proteases such as plasmin and kallikrein. The estimated plasma concentrations of aprotinin required to inhibit the different serine-proteases differ from 50 kallikrein inhibiting units (KIU)/mL for plasmin to approximately 200 KIU/mL for kallikrein. Aprotinin may therefore reduce fibrinolytic activity and thus blood loss, not only by direct inhibition of plasmin but, at higher concentration, also by inhibition of the kallikrein pathway, hereby reducing the formation of t-PA. (Figure 3) The use of aprotinin in liver transplant recipients was first described by Neuhaus et al. in 1989. These investigators observed a reduction of blood loss and transfusion requirements of 35 and 50%, respectively, in 10 patients undergoing liver transplantation, compared to historical controls. Several studies on the use of aprotinin in liver transplantation have been performed since then. However, in most of these studies retrospective control groups were used or the studies were too small to draw definite conclusions. A beneficial effect of increased surgical experience or a statistical type II error could therefore not be excluded and the efficacy of aprotinin in liver transplantation initially remained debated. More recently, the efficacy of aprotinin in reducing blood transfusion requirements during liver transplantation has been proven by well-designed, placebo-controlled, randomized, controlled trials. These prospective studies have shown that the prophylactic use of aprotinin reduces blood transfusion requirements in liver transplant recipients by about 30%. In addition to this, aprotinin has potent anti-inflammatory properties which may explain the improved hemodynamic stability, lower plasma levels of interleukin-6, and better outcome in patients who have received aprotinin,
compared to placebo.\textsuperscript{11,55-58} No increased risk of thromboembolic complications has been shown in any of the randomized controlled trials. We even found a small antithrombotic effect in an analysis of the effect of aprotinin on coagulation and fibrinolysis in liver transplantation.\textsuperscript{59,60}

\textit{\textbf{\varepsilon-Aminocaproic acid and tranexamic acid}}

The synthetic antifibrinolytics \varepsilon-aminocaproic acid (EACA) and tranexamic acid were developed in the early 1960s. The antifibrinolytic activity of these lysine analogues is caused by a competitive inhibition of the binding of plasminogen to fibrin. By blocking access to fibrin, these drugs substantially decrease the degradation of these fibrin clots. Tranexamic acid is seven times more potent and has a longer half-life than EACA. In one double-blind, randomized, placebo-controlled study, high-dose tranexamic acid was shown to be effective in reducing blood loss and transfusion requirements during liver transplantation by 46 and 31\%, respectively, when compared with placebo.\textsuperscript{\textcolor{red}{61}} In another study, a small dose of tranexamic acid was shown to adequately inhibit fibrinolysis, but no effect on transfusion requirements could be found.\textsuperscript{\textcolor{red}{62}} The number of patients in this study however was very small (16 patients in each group) and, therefore, definitive conclusions could not be drawn.

The use of EACA in liver transplant patients has been studied in only one randomized, controlled study.\textsuperscript{\textcolor{red}{63}} In this study, where patients were randomized to receive EACA, tranexamic acid or placebo, no differences in blood transfusion requirement were found between the EACA and placebo group. However, in accordance with the other study described above, mean intraoperative red blood cell requirement was 36\% lower in the tranexamic acid group, compared with placebo. A head-to-head comparison between aprotinin and tranexamic acid has been performed in only one randomized, controlled trial.\textsuperscript{\textcolor{red}{53}} Interestingly, this study did not reveal any difference in blood transfusion requirements between aprotinin and tranexamic acid-treated patients, suggesting equal effectiveness of these two drugs. It remains to be established whether the potent anti-inflammatory activities of aprotinin in addition to its antifibrinolytic activity make this drug more preferable to tranexamic acid.

\textit{\textbf{Recombinant factor VIIa}}

In recent years, the efficacy and safety of recombinant factor VIIa (rFVIIa) has been investigated during liver transplantation. rFVIIa has been shown to be effective in a variety of hemostatic disorders.\textsuperscript{8} FVIIa binds to tissue factor at the site of vascular injury and plays a central role in the activation of coagulation. In a pilot study of 6 patients treated with a single dose of rFVIIa at the beginning of liver transplantation, we have observed a significant reduction in blood transfusion requirements, compared to a matched historical control group.\textsuperscript{64,65} Two large, placebo-controlled, multicenter trials to study the efficacy and safety of rFVIIa in liver transplant recipients have recently been completed. In the first multicenter trial, reported by Planinsic et al.\textsuperscript{66}, 82 patients were randomized to receive placebo, 20, 40, or 80 \( \mu \)g/kg rFVIIa as a single dose at the start of the procedure. Although the use of a single dose regimen was in line with our initial pilot study,\textsuperscript{63} the
positive effect on perioperative RBC transfusion requirements observed in the pilot study could not be reproduced in the multicenter trial. As regards safety, there were no significant differences in thromboembolic complications among the four groups in the multicenter study. In the second multicenter trial reported by Lodge et al.\textsuperscript{67}, 183 patients were randomized to receive placebo, 80 or 120 μg/kg of rFVIIa and the doses were repeated every 2 h during the operation until 30 min before graft reperfusion. In addition, an extra dose of rFVIIa was given at the end of surgery. Despite a more sustained shortening of the prothrombin time and longer duration of detectable plasma levels of FVIIa during the operation, this trial again did not result in a significant reduction of RBC transfusion requirements in rFVIIa-treated patients compared to placebo. However, a small, but significant, increase in the percentage of patients who did not require any RBC transfusions was found in favor of the rFVIIa-treated patients. Although encouraging, the latter was not the primary endpoint of the study.

At this moment it is questionable whether rFVIIa should be used as a prophylaxis in patients undergoing liver transplantation outside the setting of prospective clinical trials.\textsuperscript{68} More work is needed to define the possible role of this new drug with attention focused on its use as a therapeutic (‘rescue’) agent rather than as a prophylactic agent.

**CONCLUSIONS**

In recent decades, blood loss and transfusion requirements in patients undergoing liver transplantation have decreased significantly. Median red blood cell transfusion requirement in adult patients undergoing a first liver transplant in our center has declined from around 20 units in the late 1980s to 2 units in the year 2003. Nowadays, approximately one-third of all adult patients undergoing a first liver transplant do not require any intraoperative transfusion of red blood cells. Extensive clinical and experimental research has led to the identification of independent risk factors for and mechanisms of increased blood loss in patients undergoing liver transplantation. Blood loss in these patients has shown to be influenced by multiple factors, such as the preoperative condition of the patient, surgical technique, organ preservation, hemostatic disorders occurring during the operation, as well as anesthesiological care. Considerable progress has been made in all of these fields, leading to this remarkable reduction in intraoperative blood loss and transfusion requirements, contributing to improved outcome after liver transplantation.
REFERENCES


Minimizing blood loss in liver transplantation


36 Miyamoto S, Polak WG, Geuenen E, Peeters PM, Jong KP, Porte RJ, Berg AP, Hendriks HG, Slooff MJ: Liver


54 Porte RJ, Slooff MJ: Aprotinin: safe and effective in all patients undergoing orthotopic liver transplantation?
Liver Transpl 2001;7:808-810.


