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Intraoperative blood transfusion requirement is the main determinant of early surgical re-intervention after orthotopic liver transplantation

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Abstract Liver transplantation is the treatment of choice in selected patients with end-stage liver disease. Postoperative complications often require surgical re-intervention. This study is a retrospective single-centre study to assess the incidence and type of surgical re-intervention during the in-hospital period after liver transplantation and to identify predictors of this re-intervention. From 1994 to 2002, 231 consecutive adult liver transplantations were performed. Re-intervention was classified as biliary, vascular, bleeding, septicaemia, re-transplantation or as miscellaneous. One hundred and thirty-nine surgical re-interventions were performed in 79 of 231 patients (34%). Septicaemia (44%) and bleeding (27%) were the most frequent indications for re-intervention, followed by biliary (10%) re-intervention. Vascular re-intervention, re-transplantation, and re-intervention for miscellaneous reasons, were performed in 7% each. Of all analysed variables (gender, age, diagnosis, acute liver failure, Child–Pugh classification, Karnofsky score, previous abdominal surgery, creatinine clearance, prothrombin time, anti-thrombin, platelet count, surgical technique, cold ischaemia time, warm ischaemia time, functional anhepatic time, anatomic anhepatic time, revascularisation time, year of transplantation, aprotinin administration, transfused platelet concentrate, and red blood cell transfusion requirements), only the number of transfused red blood cell concentrates (RBCs) was identified as a predictor of surgical re-intervention. Median RBC transfusion requirement during liver transplantation was 2.9 l (range 0–18.8 l) in the re-intervention group compared with 1.5 l (range 0–13.4 l) in the non-re-intervention group ($P < 0.001$). This study revealed intraoperative blood loss as the main determinant of early surgical re-intervention after liver transplantation and emphasises the need for further attempts to control blood loss during liver transplantation.

Keywords Liver transplantation · Re-intervention · Transfusion requirements · Blood loss

Introduction

Orthotopic liver transplantation is the treatment of choice in patients with acute or chronic liver disease and a variety of metabolic diseases [1]. The reported 1-year survival rate ranges from 70% to 85% [2, 3, 4]. Postoperative complications constitute a common cause of in-hospital morbidity and require surgical re-intervention in 27% to 55% of patients [5, 6, 7, 8, 9, 10]. Re-intervention after liver transplantation not only contributes to morbidity and mortality, but also increases the costs of this already expensive procedure [5, 11]. If the determinants of re-intervention are known, and particularly those that can be influenced, it may become possible to improve morbidity and mortality and, consequently, to reduce the costs.

The aim of this study was to identify predictors of surgical re-intervention during the in-hospital stay of patients after liver transplantation.

Patients and methods

Patients

Between January 1994 and January 2002, 251 consecutive adult patients (≥18 years) underwent primary liver transplantation at the University Medical Centre in Groningen. To obtain a homogeneous group for analysis we excluded patients who had received reduced-size liver grafts ($n=8$) and patients with combined liver–lung ($n=2$) or combined liver–kidney ($n=6$) grafts. Patients who had died during the operation ($n=4$) were also excluded. In the present study we describe the results of our retrospective analysis of the remaining 231 patients.

Operating techniques

All patients received ABO identical or compatible grafts. Selection criteria for donor livers were described earlier by our group [12]. Donor livers were harvested from haemodynamically stable, brain-dead donors. Liver function tests in donors did not exceed a three-fold increase of the upper limit of normal ranges. All donor livers were perfused and stored in cold (4°C) University of Wisconsin solution. Implantation techniques changed during the study period. Before 1994 the conventional technique, as described by Starzl, was exclusively used [13]. The native liver of the recipient was removed en bloc with the retro-hepatic inferior caval vein. During the anhepatic phase a venovenous bypass was used, as described by Shaw et al. [14], or as modified by our group [15]. After January 1994 the implantation technique was gradually replaced by the piggyback technique [16]. With the latter technique, the inferior caval vein of the recipient is left in situ and the supra hepatic cuff of the donor's inferior caval vein is anastomosed to the recipients caval vein, while no venovenous bypass is used. Overall, 116 patients were operated on by the conventional technique and 115 patients by the piggyback technique (Fig. 1).

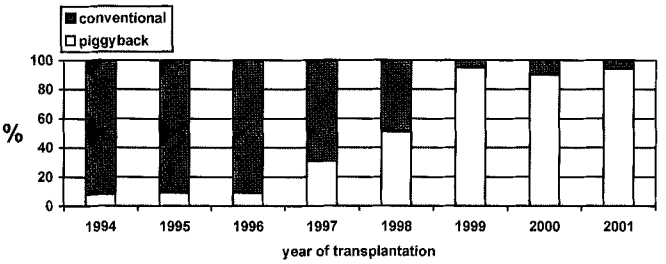

Fig. 1 Implantation techniques as applied in 231 liver transplant patients over the period 1994–2001

Anti-microbial prophylaxis

Until September 2000 perioperative prophylaxis consisted of selective bowel decontamination (amphotericin B 500 mg, tobramycin 50 mg, and colistin 100 mg). Additionally, tobramycin (3 mg/kg per 24 h, i.v.) and cefuroxime (1,000 mg/24 h, i.v.) were perioperatively administered for 48 h. After September 2000 perioperative prophylaxis consisted of amoxicillin/clavulanic acid (2,000 mg t.i.d, i.v.) and ciprofloxacin (400 mg b.i.d, i.v.). Patients allergic to penicillin received imipenem (1,000 mg t.i.d, i.v.). All patients received oral acyclovir (200 mg q.i.d.), for the first 4 weeks after transplantation, as herpes simplex prophylaxis. If the donor and/or recipient was seropositive for cytomegalovirus infection, ganciclovir (1,000 mg t.i.d., orally) was started at postoperative day (POD) 10 and continued for 3 months.

Immunosuppression

Patients with autoimmune diseases (autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis) received immunosuppressive triple therapy with prednisolone, azathioprine and cyclosporin A. All other patients received a double immunosuppressive regimen, containing prednisolone and either tacrolimus or cyclosporin A.

Postoperative surveillance

To assess the patency of the graft vessels, we performed serial Doppler ultrasonography at PODs 1, 3 and 7, or

on demand if impaired graft function became overt [17]. A liver biopsy was done at the end of the first postoperative week. A cholangiogram, to control for biliary complications, was performed via the biliary drain in the second postoperative week. In case of fever, cultures were taken from all drains, urine, sputum, bile and ascites. If indicated, an abdominal CT scan was done.

Definitions

The observation period of patients started at the time of their primary liver transplantation and ended at discharge or at in-hospital death. Outcome variable was the number of patients with surgical re-intervention during the observation period. Re-intervention was categorised as biliary, vascular, bleeding, septicaemia, re-transplantation, or as re-intervention for other, i.e. miscellaneous, intra-abdominal complications. *Biliary re-intervention* was re-operation for bilomas, leakage from the anastomotic site, or stenosis or necrosis of the bile ducts. *Vascular re-intervention* was re-operation for thrombosis of the hepatic artery or the portal vein, and torsion or compression of the outflow tract. *Re-intervention for bleeding* consisted of surgery for intra-abdominal blood loss after transplantation or for removal of haematomas or gauzes. These gauzes had been used for packing, as a temporary measure to stop intraoperative bleeding. *Re-intervention for septicaemia* was re-intervention for evacuation of intra-abdominal abscesses or rinsing of the peritoneal cavity in case of diffuse peritonitis. *Re-transplantation* was defined as a second liver transplantation within the hospitalisation period succeeding the primary transplantation. *Re-intervention for miscellaneous intra-abdominal complications* included re-operation for bowel obstruction, leaking or perforated feeding jejunostomy, bleeding peptic ulcer, appendicitis and wound dehiscence.

Patients' characteristics that were analysed included gender, age, primary disease (cholestatic versus non-cholestatic), acute liver failure (ALF), Child–Pugh classification, Karnofsky score, previous upper-abdomen operations and kidney function. Cholestatic liver diseases included primary biliary cirrhosis, primary sclerosing cholangitis and secondary biliary cirrhosis. Non-cholestatic liver diseases included all other diagnoses. The Child–Pugh classification A, B or C represents the severity of liver disease [18]. The Karnofsky score characterises the condition of the patient, ranging from poor (10 points) to good (100 points) [19]. Previous upper-abdomen surgery included major operations of the liver and/or biliary tract and portal systemic decompression procedures for portal hypertension. The creatinine clearance was used as a measure for kidney function. Also analysed were the prothrombin time (PT), the anti-thrombin (AT), and the platelet count. The surgical characteristics analysed were: surgical technique (conventional or piggyback); cold ischaemia time (CIT); warm ischaemia time (WIT); functional anhepatic phase (FAHP); anatomical anhepatic phase (AAHP); revascularisation time (REVT); year of transplantation; aprotinin administration; transfused platelet concentrates; and red blood cell transfusion requirements; CIT was defined as the time from in situ flushing of the graft in the donor to removal of the graft from ice before implantation, WIT as the time between removal of the graft from ice and recirculation in the graft via the portal vein and/or hepatic artery. The FAHP started as soon as both portal vein and hepatic artery in the recipient were closed and ended at reperfusion of the graft, the AAHP started at removal of the native liver and ended at reperfusion of the graft. REVT was defined as the time from removal of the graft from ice until restoration of the circulation of both portal vein and hepatic artery.

Transfusion protocol

The transfusion regimen was standardised. Blood loss was compensated for by transfusion of allogeneic packed red blood cells (with buffy-coat) or autologous blood cells to maintain haematocrit values between 0.25 and 0.30 The number of red blood cell concentrates (RBCs) that were transfused represented blood loss. Measurement of blood loss is considered to be less accurate than requirement of RBC transfusion, because of dilution of fluid in suction containers by ascites and intraperitoneal hypersecretion, in addition to practical difficulties. One unit of allogeneic (bank) blood or autologous (cell saver) blood had a volume of 250 ml and its haematocrit amounted 0.70. Six units of platelet concentrates were given when platelet counts dropped below 50×10^9/l. Before October 2000 only four patients out of 188 received aprotinin in a variable dose. Afterwards, all patients except five received aprotinin in a high dose, i.e. an i.v. loading dose of 2×10^6 kIU, followed by a continuous i.v infusion of 1×10^6 kIU/h until 2 h after graft reperfusion. All patients received a lower body warm touch and an oesophagus-heating device until 1999, since when a lower body and upper body warm touch have been used. With these measures all patients had a central body temperature ranging between 36°C and 37°C.

Statistics

Patients with surgical re-intervention and those without were compared with respect to patients' and surgical characteristics. Qualitative variables were analysed by the χ^2 test or Fisher's exact test, quantitative variables by Students *t*-test or the Mann–Whitney U test when appropriate. *P* values < 0.05 were considered statistically

significant; all tests were two-sided. We performed multiple logistic analysis to identify predictors of re-intervention. All variables that showed a P value <0.15 by univariate analysis were included in a multiple logistic model.

Results

Patients' and surgical characteristics are summarised in Table 1. Overall, median in-hospital stay (the observation period) was 37 days (range 3–201 days). Surgical re-intervention was performed in 79 out of 231 patients (34%) (Table 2). These patients underwent 139 re-intervention procedures (range 1–11 per patient). Thirty-four patients underwent a second re-intervention, and 26 had three or more re-interventions. The first re-intervention was performed at a median of 9 days (range 0–116 days) after primary liver transplantation. Septicaemia (61 procedures in 36 patients) and bleeding (36 procedures in 30 patients) were the most common indications for surgical re-intervention. Re-intervention for miscellaneous intra-abdominal complications (nine procedures in nine patients) encompassed surgery for wound dehiscence ($n=4$), ileus ($n=2$), removal of a laparotomy pad ($n=2$), and surgery for suture of a bowel perforation ($n=1$).

Of 79 patients who had a first re-intervention, 34 (44%) underwent a second. Main reasons for the second one were also septicaemia ($n=20$) and bleeding ($n=6$). Of 20 patients with a second re-intervention for septicaemia, nine had undergone prior re-intervention for this reason, while in eight patients bleeding necessitated the first re-intervention.

In-hospital mortality rates were 19% in the re-intervention group and 6% in the non-re-intervention group ($P=0.003$). These were 17% and 21% in patients with a first re-intervention for septicaemia and bleeding, respectively. The mortality rate after the in-hospital stay was the same in both groups, 7% at follow-up to 4.2 years after liver transplantation. Patients in the re-intervention group stayed significantly longer in hospital (median 50 days, range 3–201 days) than patients in the non-re-intervention group did (median 32 days, range 3–151 days) ($P<0.001$).

The results of the statistical analysis are summarised in Table 3. Of all variables tested, including year of transplantation ($P=0.451$, not mentioned in Table 3), intraoperative transfusion of platelet concentrate and intraoperative RBC transfusion requirements showed a statistically significant difference between the re-intervention group and the non-re-intervention group. Of patients that had undergone a re-intervention procedure, 51% received transfusion of platelet concentrates, compared to 22% in the non-re-intervention group ($P=0.016$). Median RBC requirement was 2.9 l (range 0–18.8 l) in the re-intervention group versus 1.5 l (range 0–13.4 l) in the non-re-intervention group ($P<0.001$). In the multivariate analysis only intraoperative RBC transfusion requirements was identified as an independent predictor of postoperative re-intervention ($P<0.001$).

Table 1 Demographic characteristics of 231 donor liver recipients and details of transplantation. Continuous variables are presented as median (range) and categorical variables as number (percentage)

Recipients		Transplantation	
Gender		Technique	
Male	131 (57)	Conventional	116 (50)
Female	100 (43)	Piggyback	115 (50)
Age (years)	46 (18–68)	CIT (h:min)	10:00 (3:23–20:05)
Primary disease		WIT (h:min)	0:57 (0:20–2:09)
Cholestatic	61 (26)	FAHP (h:min)	2:20 (0:48–10:25)
Non cholestatic	170 (74)	AAHP (h:min)	1:35 (0:39- 5:17)
Acute liver failure	18 (8)	REVT (h:min)	1:33 (0:31 -3:40)
Child–Pugh classification[a]		Platelet requirement[a]	
A	42 (19)	Yes	92 (40)
B	85 (38)	No	138 (60)
C	97 (43)	Aprotinin administration	
Previous operation[a]		Yes	43 (20)
Yes	70 (30)	No	188 (80)
No	154 (67)	RBC requirement (l) 2.0 (0–18.8)	
Karnofsky score (points)	60 (10–90)		
Creatinine clearance (ml/min)	91 (8–261)		
Prothrombin time (s)	18.5 (11.2–120)		
Anti-thrombin (%)	42 (3–140)		
Platelet count ($\times 10^3$/mm^3)	84 (14–542)		

[a]Retrospective data not traced in all patients

Table 2 Classification of re-intervention and in-hospital mortality in 231 patients after primary liver transplantation

Type of re-intervention	First re-intervention	Second[a] re-intervention	Third[a] or more re-intervention	Total number of re-interventions
Re-intervention	79	34	26	139
Biliary	10	2	2	14
Vascular	9	1	0	10
Bleeding	28	6	2	36
Septicaemia	23	20	18	61
Re-transplantation	5	1	3	9
Miscellaneous	4	4	1	9
No re-intervention				152

[a]In patients with more than one re-intervention, the type of succeeding re-intervention varied

Table 3 Analysis of characteristics related to surgical re-intervention after liver transplantation performed in 79 out of 231 patients

Variable	Category	Patients with re-intervention Number (%)	Patients with no re-intervention Number (%)	*P*
Gender	Male	42 (53)	89 (59)	0.49
	Female	37 (47)	63 (41)	
Primary disease	Cholestatic	21 (27)	40 (26)	1.00
	Non-cholestatic	58 (73)	112 (74)	
Acute liver failure	No	73 (92)	140 (92)	1.00
	Yes	6 (8)	12 (8)	
Child–Pugh classification	A	12 (16)	30 (20)	0.58
	B	32 (42)	53 (36)	
	C	32 (42)	65 (44)	
Previous upper-abdomen operation	No	53 (68)	101 (69)	0.88
	Yes	25 (32)	45 (31)	
Surgical technique	Conventional	41 (52)	75 (49)	0.78
	Piggyback	38 (48)	77 (51)	
Platelets transfused	No	38 (49)	100 (66)	0.02
	Yes	40 (51)	52 (34)	
Aprotinin administration	No	66 (84)	122 (80)	0.60
	Yes	13 (16)	30 (20)	
		Median (range)	Median (range)	*P*
Age (years)		47 (18–68)	46 (18–66)	0.56
Karnofsky (points)		60 (10–90)	70 (10–90)	0.53
Clearance (ml/min)		93 (8–199)	89 (13–261)	0.97
Prothrombin time (s)		18.2 (12.5–57.0)	18.8 (11.2–120)	0.79
Anti-thrombin (%)		42 (10–135)	42 (3–140)	0.93
Platelet count ($\times 10^3/mm^3$)		79 (14–542)	90 (16–509)	0.10
CIT (h:min)		10:21 (4:09–16:00)	9:54 (3:23–20:05)	0.54
WIT (h:min)		0:58 (0:20–2:09)	0:56 (0:27–1:54)	0.57
FAHP (h:min)		2:27 (0:48–7:19)	2:19 (0:49–10:25)	0.42
AAHP (h:min)		1:35 (0:44–5:17)	1:35 (0:39–4:38)	0.47
REVT (h:min)		1:34 (0:48–3:40)	1:33 (0:31–3:38)	0.51
RBC transfused (l)		2.9 (0–18.8)	1.50 (0–13.5)	< 0.001
RBC transfused—gauzes[a] (l)		2.1 (0–16.0)	1.50 (0–13.5)	0.007

[a]Excluding patients who underwent re-intervention to remove gauzes

In 16 out of 28 patients (57%) who had undergone a first re-intervention for bleeding, this re-surgery was necessary to remove gauzes, left behind during the primary liver transplantation to stop massive bleeding by tamponade. The difference in RBC transfusion requirement between the two groups remained statistically significant when these patients were excluded from analysis: median blood loss 2.1 l (range 0–16.0 l) in the re-intervention group versus 1.5 l (range 0–13.4 l) in the non-re-intervention group ($P = 0.007$).

Discussion

This study showed that 34% of patients who underwent liver transplantation needed at least one surgical re-intervention during the initial hospitalisation period. Of all re-intervention procedures, 40% and 24% were due to septicaemia and bleeding, respectively. Intraoperative transfusion of RBC, i.e. blood loss, was the sole predictor of surgical re-intervention after orthotopic liver

transplantation. Patients who had undergone re-intervention had a three-times higher mortality during the observation period (19% versus 6%, $P=0.003$) and stayed significantly longer in the hospital (median 50 versus 32 days, $P<0.001$) than did patients who had not undergone re-intervention.

Previous reports have shown a relationship between intraoperative blood loss and morbidity and mortality, as well as a longer stay in the intensive care ward [20, 21, 22, 23]. This study clearly indicates the relation between intraoperative blood loss, surgical re-intervention during the in-hospital stay after liver transplantation, and a prolonged in-hospital stay. The requirement for additional operating procedures after liver transplantation is associated with high costs [24], and length of in-hospital stay has been shown to be the most important determinant of costs after liver transplantation [25]. As we found surgical re-intervention to be mainly related to more intraoperative blood loss and a prolonged in-hospital stay, they were associated with higher costs.

Many studies have reported allogeneic blood transfusions to be associated with adverse effects in recipients [26]. This raises two questions. First, are RBC transfusions a marker of disease, i.e. do ill patients require more RBC transfusions than their "healthier" cohorts do?

Except for higher RBC transfusion requirements in our study, the re-intervention group and non-re-intervention group did not differ from each other; in particular, the preoperative Child–Pugh classification and clotting profile were not different. Hébert et al. [27] found, in a multicentre, randomised, controlled, clinical trial, that a restrictive strategy of RBC transfusion in critical ill patients was at least as effective as, and possibly superior to, a liberal transfusion strategy. This suggests that transfusion of RBC causes the adverse effects and does not indicate some (still unknown) marker of disease. However, it is almost impossible to separate out the direct impact of RBC transfusion in these complex clinical circumstances.

The second question, is RBC transfusion the cause of a poorer outcome and by what mechanism, is also difficult to answer. Currently, the risk of transmission of infectious diseases through transfusion is low, because of effective preventive strategies. However, every blood transfusion interferes with the immune system of the recipient, including clinically significant immunosuppression [28]. This transfusion-associated immunomodulation (TRIM) has been linked to a reduced rejection rate in the setting of renal transplantation [29], but possible deleterious effects of TRIM include increased prevalence of cancer recurrence and bacterial infections [26, 28].

Recently, Hébert et al. found RBC leucoreduction to be associated with decreased mortality as well as decreased fever episodes in high-risk patients [30]. This might explain the high incidence of septicaemia found in our group with high (not leucoreduced) RBC transfusion requirements. Until 2001 all patients who required RBC transfusion received either allogeneic (bank) blood or a combination of autologous (cell saver) blood and allogeneic blood. After 2000 all patients received only allogeneic blood. This data does not allow us to differentiate in our analyses between the effects of autologous and allogeneic blood transfusions separately. While considerable data have accumulated in the attempt to unravel the mechanism of TRIM, the precise mechanisms and clinical impact have not yet been elucidated [26].

From the presented data it is obvious that attempts to reduce transfusion requirements, i.e. blood loss, are warranted, to lower the incidence of re-intervention and, consequently, to improve in-hospital morbidity and mortality after liver transplantation and, in addition, to reduce the costs. These attempts might be addressed to the restoration of haemostasis, and further improvement of surgical and anaesthetic techniques. Haemostatic drugs such as aprotinin and recombinant factor VIIa should be considered. Aprotinin reduces blood transfusion requirements during liver transplantation by 30% to 40% [31, 32]. In the present study there was no difference in the number of re-intervention procedures between patients with or without administered aprotinin. This might be explained by the small number of patients who received aprotinin.

The limited experience with recombinant factor VIIa, though promising, justifies further studies [33]. However, there is no doubt that all pro-haemostatic measures potentially increase the risk of thrombosis. An increased incidence of hepatic artery or portal vein thrombosis would clearly be unacceptable, as these are associated with increased morbidity and mortality [9]. This should be weighed against the risk of bleeding and surgical re-intervention. Appropriate monitoring of haemostatic variables, to render an optimal balance between hypocoagulation and hypercoagulation, seems to be crucial. Thromboelastography enables "bed-side" assessment of the whole clotting process and provides information about interactions of blood cells, pro-coagulants and anticoagulants [34]. Hence, this test has potential advantages when compared with standard coagulation tests. Though it has been stated that thromboelastography is indispensable for the monitoring and correction of haemostasis [35], more studies need to be done to obtain convincing evidence that blood loss is, indeed, reduced if this technique is applied.

In conclusion, the intraoperative requirement for red blood cell transfusion was the main determinant of early in-hospital surgical re-intervention after liver transplantation. This finding emphasises the need for further attempts to control blood loss during liver transplantation.

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