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Mortality after orthotopic liver transplantation

An analysis of the causes of death in the first 50 liver transplantations in Groningen, The Netherlands

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Abstract. An analysis was made of the causes of death in 22 of 50 patients receiving consecutive orthotopic liver transplants. A close look at the fatal course of these patients revealed three major patterns: surgical complications (27%), pathology of the hepatic artery anastomosis (23%), and cholestasis (32%). Technical factors were the major reasons for excessive peroperative blood loss, and not the coagulopathy accompanying the liver disease. The etiology of hepatic artery thrombosis is not known. It leads to irreversible damage of the graft, causing death due to acute hepatic failure or to cholangitis and sepsis. The only way to treat patients with this complication is retransplantation. Several factors can induce cholestasis. Retrospectively, it appears that this was mostly due to inappropriate immunosuppression, often a result of the difficult differential diagnosis between rejection and viral infection. Recognition of these three basic patterns should enable us to anticipate their subsequent complications. This may lead to a reduction in morbidity and mortality after liver transplantation.

Key words: Liver transplantation - Blood loss - Hepatic artery thrombosis - Cholestasis - Mortality.

Orthotopic liver transplantation (OLT) was established as an accepted treatment for end-stage liver disease after the 1983 National Institute of Health consensus meeting on this subject. At that time, perioperative mortality rates of 20%-40% were thought to be acceptable, given the low quality of life and often imminent death of the recipients [16]. Improved surgical and anesthetic techniques, better intensive care facilities, the use of cyclosporine A as a main immunosuppressant, and the possibility of retransplantation in cases of graft failure have had a beneficial impact on patient survival, as reported by Starzl et al. [27] and Rolles and Calne [20].

Despite this progress, mortality after liver transplantation remains a considerable problem. Experienced centers, as well as newer ones, still report an overall mortality rate in the first year of between 25% and 40% [2, 4, 5, 26, 31]. Death after liver transplantation is seldom caused by a single event but more often results from several related complications. Coagulopathy, infection, peptic ulceration, chronic rejection, and multiple organ failure are the most commonly reported causes of death [4, 7, 14]. Yet, these causes are terminal rather than etiological events. This notion prompted us to analyze the mortality in our series. The aim of the study was to investigate whether, behind these variable clinical presentations of the terminal course, certain basic patterns could be defined that lead from a basic event to the ultimate death of the recipient.

Patients and methods

This study analyzes mortality in the first 50 patients who underwent 55 OLTs at the University Hospital in Groningen, The Netherlands between March 1979 and September 1986. Forty-four were adult patients - 12 men and 32 women - with a mean age of 39 years (range 17-57). Six were children with a mean age of 4.5 years (range 1-11).

Patient selection

All patients were selected for the procedure by the same physicians and according to a strict protocol described in detail elsewhere [19]. After referral of liver transplant candidates, a com-

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Table 1. Original disease

Type	*N*
Chronic active/inactive cirrhosis	22
Primary biliary cirrhosis	17
Biliary atresia	4
Alpha-1 antitrypsine deficiency	2
Secondary biliary cirrhosis	1
Hepatocellular carcinoma	1
Budd-Chiari syndrome	1
Hemangioma	1
Erythropoietic protoporphyria	1
Total	50

plete medical and hepatological work-up was performed. The stage of liver disease was evaluated and renal sodium and water handling were checked. The clinical condition was then assessed, especially cardiopulmonary performance. Before transplantation, gastroscopy was performed to detect esophageal varices and peptic ulcers. In order to visualize arterial and portal circulation, angiography was performed. Foci for infection were screened. A general bacteriological surveillance was done and a carrier status *(Staphylococcus aureus)* was treated. During the preoperative work-up, three blood transfusions were given, as described in the Eurotransplant pretransplant blood transfusion protocol. The original diseases of the patients are listed in Table 1. There were five retransplantations, all second grafts in adult patients. The indications for retransplantation included chronic rejection in four cases and necrotic bile ducts and intrahepatic abscesses in one case.

Operative techniques

Our technique of liver harvesting and conditioning of the donor has been described elsewhere [8]. Basically, the organ is taken from a stable, brain-dead, heart-beating donor after in situ cooling with Eurocollins solution and preserved in the same solution for periods up to 9 h. The implantation procedure is similar to that described by Starzl [25]. In only five cases was the venovenous bypass used.

Postoperative management

Perioperative infection prevention was done by selective bowel decontamination with oral doses of polymixin B, amphotericin B, and tobramycin during the first 3 weeks and with parenteral cephalosporins and tobramycin for the first 48 h as described by Van der Waay [29]. Immunosuppression consisted of both prednisolone and azathioprine. Prednisolone was started postoperatively with 200 mg per day and slowly tapered. The median daily prednisolone dose at 1 month was 40 mg and at 1 year, 20 mg. The azathioprine dose was 125-150 mg per day. Additionally, some patients received 1000 mg methyl prednisolone or 100 mg cyclophosphamide just before and during the first 3 days after OLT. Rejection episodes were treated with an increase in daily steroid dosage up to 100-200 mg prednisolone. Because of the favorable experience with this conventional immunosuppressive regimen reported by Krom et al. [15], ALG/ATG, cyclosporine A, and monoclonal antibodies were not used in this series.

Postoperative liver functions were monitored and standard bacteriological and viral surveillances were performed. Viral infection was suspected when fever, arthralgia or myalgia, or herpetic lesions developed. The diagnosis of viral infection by cytomegalovirus (CMV) or herpes simplex virus (HSV) was established by serology (fourfold titer rise or seroconversion). Protocol biopsies of the graft were taken during donor hepatectomy, after revascularization of the graft, on day 7, at discharge, and at yearly intervals. In addition, nonprotocol biopsies were taken to study graft function disturbances.

Acute rejection was suspected when fever, leukocytosis, eosinophilia, and rise of liver tests developed [20]. The clinical diagnosis was confirmed by a liver biopsy showing portal mononuclear cell infiltrates, venous endotheliitis, and inflammatory damage to small bile ducts [24].

Chronic rejection was suspected when patients showed a persisting, severe, cholestatic, biochemical profile in the absence of other causes of graft dysfunction, such as biliary obstruction, viral disease, or thrombosis of the hepatic artery. Histologically, chronic rejection was diagnosed when obliterative vasculopathy in medium and large branches of the hepatic artery was observed with or without a diminished number of small bile ducts [30]. All recipients underwent post-transplant angiography when deterioration of graft function indicated possible vascular complications and/or at patient discharge and at 1 year after OLT. On all but one deceased patient, an autopsy was performed.

A statistical analysis was not performed because of the descriptive nature of this retrospective clinical study.

Results

The actuarial survival of the 50 patients at 1, 2, and 5 years is 58%, 56%, and 48%, respectively. Twenty-two patients (44%) died, 18 of them within 1 year after OLT.

In Table 2, the clinical presentation of the cause of death in the individual cases is listed, together with the intervals between transplantation, the onset of the clinical problems, and the time of death, and the factors contributing to the fatal outcome. Three basic patterns can be recognized (last column). The first basic pattern involves surgical complications with excessive blood loss, leading to exsanguination, sepsis, or multiorgan failure ($N=6$). The second basic pattern is hepatic artery pathology, leading to acute hepatic failure or bile duct necrosis, with or without sepsis ($N=5$). The third basic pattern is chronic cholestasis, ultimately leading to liver insufficiency, infection, and peptic ulceration, with or without gastrointestinal bleeding ($N=7$).

Four patients do not fit into any of these three basic patterns and constitute an "unclassified" group.

Surgical complications with excessive blood loss

Six patients died as a consequence of peroperative complications (Table 3). The majority of these patients were in Child-Pugh class C, which implies an already impaired coagulation status. This is reflected in high blood loss already in the preanhepat-

Table 2. Basic patterns, contributing factors, and clinical presentation of death. IVC, Inferior caval vein; DIC, diffuse intravascular coagulation; DU, duodenal ulcer; EPP, erythropoietic protoporphyria; HAT, hepatic artery thrombosis; aza-allergy, azathioprine allergy

OLT no.	Clinical presentation of cause of death	Time of		Contributing factors	Basic patterns
		Onset	Death		
1	Exsanguination	0	0 peroperative	Technical factors (IVC)	Surgical complication
4	Ileus/sepsis	0	2 weeks	Ongoing DIC	
9	Multiple organ failure	0	5 weeks	Splenic rupture	
20	Exsanguination	0	0 peroperative	Technical factors (IVC)	
21	Exsanguination	0	0 peroperative	Large donor liver	
46	Exsanguination	0	0 peroperative	Portacaval shunt	
6	Acute hepatic failure	2 weeks	2 weeks	Thrombosis	Hepatic artery pathology
12	Acute hepatic failure	1 week	1 week	Thrombosis	
19	Abdominal bleeding/bleeding DU	6 weeks	6 weeks	Aneurysm	
26	Necrotic bile ducts/sepsis	12 weeks	4 months	Thrombosis	
29	Necrotic bile ducts/sepsis	7 weeks	11 months	Thrombosis	
14	*Aspergillus pneumonia*	2 weeks	4 months	CMV/rejection	Cholestasis
24	Pneumonia/sepsis	7 weeks	3 years	CMV/rejection	
28	Bleeding DU/abscesses	2 weeks	6 months	CMV/rejection/recurrence EPP	
31	Bleeding DU	2 weeks	15 months	CMV/rejection/HAT	
35	Chronic liver failure/coma	7 weeks	4 months	rejection/HAT/aza-allergy	
39	CMV pneumonia	2 weeks	11 months	CMV/rejection	
41	Sepsis	2 weeks	3 months	Thrombosis superior mesenteric vein	
18	Suicide	15 months			
23	Acute hepatic failure	1 week	1 week		
25*	Recurrent lung emboli/cardiac failure	12 weeks	3.5 years		
33	Acute hepatic failure (CMV)	1 week	5 weeks		

Table 3. Preoperative stage of liver disease and perioperative blood loss (liters whole blood)

Child-Pugh classification	OLT 1 C	OLT 4 C	OLT 9 A	OLT 20 C	OLT 21 C	OLT 46 B
Preanhepatic phase	7	7	2	6	5	7
Anhepatic phase	12	8	9	5	15	44
Postanhepatic phase	21	17	3	28	14	48
Total	30	32	14	39	34	99

ic phase of the operation. Table 3 also shows that the greater amount of blood loss occurred in the anhepatic and postanhepatic phases of the operation. In OLT 1, construction of the suprahepatic caval anastomosis was hampered by continuous bleeding from the hepatectomy surface. A leakproof anastomosis was not achieved, leading to severe blood loss after recirculation. In OLT 9, a splenic rupture led to massive peroperative blood loss during the anhepatic phase. Although the patient survived the operation, she died 5 weeks later due to multiple organ failure, a bleeding cecal ulcer, and sepsis. In OLT 20, sutures tore off the diaphragmatic caval vein cuff, leading to uncontrollable leakage after recirculation of the graft. In OLT 21, the donor liver was too big for the recipient, causing insurmountable problems with the supra- and infrahepatic caval anastomoses and leading to exsanguination of the patient. In OLT 46, the portacaval shunt ruptured during the preparatory phase of the recipient hepatectomy. Although the implantation of the graft could be completed, the patient became exsanguinated due to intractable coagulopathy induced by the blood loss.

In OLT 4, the considerable blood loss during the preanhepatic phase was attributed to a diffuse intravascular coagulation (DIC)-like syndrome. This was treated with intravenous heparin. Bleeding persisted per- and postoperatively, both abdominally and later intracranially. Ultimately, the patient died, due to a paralytic ileus and sepsis 2 weeks after the transplant.

Pathology of the hepatic artery anastomosis

Five patients (OLTs 6, 12, 19, 26, and 29) died due to pathology of the arterial anastomosis. OLT 6 developed acute hepatic failure 2 weeks after OLT. Multiorgan failure occurred and the patient died. At autopsy, a thrombosed hepatic artery and multiple

infarctions of the liver were found. OLT 12 died within 5 days due to acute hepatic failure of the graft with diffuse bleeding, hypoglycemia, hypothermia, anuria, and coma. An autopsy revealed hepatic artery thrombosis and massive necrosis of the liver. OLT 19 died from a ruptured aneurysm of the hepatic artery anastomosis with intra-abdominal blood loss, together with a concomitant bleeding duodenal ulcer. In OLTs 26 and 29, sepsis due to necrotic bile ducts and/or intrahepatic abscesses and cholangitis was the cause of death. In both cases, angiography revealed a thrombosis of the arterial anastomosis soon after OLT.

Chronic cholestasis

In seven patients, cholestasis developed in an early phase after liver transplantation. All patients died at different intervals due to such sequelae of the chronic cholestasis as infection, peptic ulcer, liver failure, or a combination of these factors.

Unravelling the cause of cholestasis can be difficult. Rejection, viral infection, drug toxicity, sepsis, vascular thrombosis, and recurrence of the original disease all have to be considered. In four patients (OLTs 28, 31, 35, and 39), acute rejection observed at the end of the first week was not treated, resulting in ongoing rejection and leading to cholestasis. The immunosuppressive regimen during the first 2 weeks after OLT was thought to be sufficient to absorb such an early rejection. In two other patients (OLTs 14 and 24), repeated rejection episodes were misdiagnosed as viral infections and treated as such by tapering the immunosuppression. In OLT 35, azathioprine allergy was a concomitant factor. Azathioprine was replaced by the less effective immunosuppressive drug cyclophosphamide. Septic abdominal complications after gastric resection for a bleeding peptic ulcer in case OLT 28 and the very poor condition of patient OLT 41 after an unsuccessful first graft were the reasons for suboptimal immunosuppressive dosages.

In four patients, other factors, such as a possible recurrence of erythropoietic protoporphyria in the graft (OLT 28) and vascular thrombosis (OLTs 31, 35, and 41; see Table 2) were thought to have contributed to cholestasis.

The central problem with all of these patients was that several different factors made it necessary to reduce the immunosuppressive scheme, resulting in a state of chronic underimmunosuppression.

In only four of the seven patients could the diagnosis of chronic rejection be proven histologically. In three patients, the classic histological picture of chronic rejection as described by Wight [30] was not complete.

Unclassified patients

The course of four patients was difficult to classify. OLT 18 committed suicide 15 months after her initially complicated, but ultimately successful, liver transplantation. OLT 23 died 5 days after transplantation due to sustained bleeding from multiple stress ulcers in the stomach and defective coagulation together with liver failure. An autopsy revealed massive necrosis of the liver with patent vascular anastomoses but no cholestasis or rejection. A liver biopsy, taken 1 h after revascularization of the graft, showed vital liver tissue, and liver tests of the donor were normal. OLT 25 died 3.5 years after liver transplantation. She had a very complicated postoperative course due to an extrahepatic bile duct stricture. Correction by a hepaticojejunostomy was complicated by intra- and extrahepatic abscesses and a colonic fistula. During the next 2 years, several episodes occurred with dyspnea and tachycardia caused by lung emboli. Notwithstanding treatment with anticoagulants, pulmonary hypertension developed, resulting in death from cardiac failure. OLT 33 died 5 weeks after transplantation due to acute hepatic failure. Twenty days after OLT, a viral hepatitis developed and immunosuppression was withdrawn. An autopsy revealed CMV pneumonitis, hepatitis, and myocarditis. No signs of vascular thrombosis or rejection were observed.

Discussion

The aim of this study was to see whether, behind the various clinical presentations of the fatal course of liver transplant patients, certain basic events could be detected. In our analysis, three factors emerged that initiated a devastating chain reaction. These factors were surgical complications with excessive blood loss, hepatic artery pathology, and chronic cholestasis. Blood loss has always been a problem during liver transplantation. On the one hand, it is directly related to the preoperative stage of liver disease; on the other, it is directly related to mortality [4, 10, 14, 26]. Our experience has shown surgical complications to be the major cause of the observed blood loss (Table 2). Coagulopathy aggravates blood loss when technical complications arise.

The prevention of excessive blood loss is an important issue in liver transplantation. In this respect, the selection of patients appears to play an important role. Patients who have undergone previous upper abdominal operations (e.g., OLT 46) run the rsik of losing excessive amounts of blood because of the many vascularized adhesions [4, 14, 21, 26]. Kirby et al. [14] recommend the avoidance of abdomi-

nal surgery, especially portacaval shunt surgery, in future liver transplantation candidates. A poor coagulation status should be recognized during the recipient work-up. Impaired renal sodium and water handling is an important indicator for the coagulation status, as was reported by Haagsma et al. [10]. Furthermore, the venovenous bypass described by Shaw et al. [22] may reduce blood loss during the anhepatic phase of the operation. In addition to the reduction of the peroperative blood loss, Shaw et al. reported a better postoperative renal function and an improved 30-day survival in patients with the venovenous bypass as compared to patients without [22]. In OLT 9, the venovenous bypass could have prevented the splenic rupture and its subsequent complications by effectively reducing the portal pressure during the anhepatic phase of the operation. Careful matching of recipient and donor liver size can also prevent excessive blood loss. If the donor liver is too large for the recipient, as in OLT 21, the size of the donor liver can be reduced by segmentectomies. Mortality and morbidity appear to be the same in partial-liver grafting and in whole-liver grafting [12].

Thrombosis of the arterial anastomosis soon after transplantation can lead to necrosis of the graft or hepatic failure. Our report on the importance of a patent arterial anastomosis for graft survival [13] is confirmed by several other authors [3, 28, 32]. When hepatic artery thrombosis occurs soon after transplantation, as in OLTs 6 and 12, acute hepatic failure ensues. Other sequelae of early hepatic artery thrombosis are intrahepatic abscess formation and bile duct necrosis. Retransplantation is the only treatment option for symptomatic hepatic artery thrombosis [4, 7, 14, 21, 26]. Recently, Otte et al. reported successful extrahepatic duct reconstruction by a Roux-en-Y hepaticojejunostomy in such patients [17], but the long-term efficacy of this approach remains to be seen.

The cause of hepatic arterial thrombosis remains largely unclear. Technical factors, such as kinking of the artery or intimal lesions, explain only some of the cases. Groth et al. suggested that rejection may be implicated [9]. Swelling of the graft and vascular narrowing due to rejection may cause outflow obstruction of the hepatic artery and thrombosis of the hepatic arterial anastomosis. Kirby et al. [14] and Zajko et al. [32] report angiographies in patients (one case and several cases, respectively) with graft rejections which show a poor peripheral filling and attenuation in the size and number of intrahepatic arteries, resulting in a decreased arterial flow. Further studies are required to confirm the connection between rejection and hepatic artery thrombosis.

A single cause of cholestasis is unlikely. Only in four of our seven patients could chronic rejection be proven histologically, which makes it probable that factors other than underimmunosuppression play an additional role. One could well be vascular pathology. Two patients with hepatic aratery thrombosis were represented in this chronic cholestasis group. Both cases had thrombosis of the arterial anastomosis in a late phase after transplantation. They presented with a completely different clinical picture (cholestasis) than the patients with early hepatic artery thrombosis (acute hepatic failure, necrosis of the bile duct, hepatic abscesses, sepsis).

Chronic cholestasis poses a challenge for a proper clinical diagnosis. Ultrasonography, cholangiography, and arteriography are useful tools in this respect. Ultrasonography can indicate such intrahepatic pathology as abscesses or dilated bile ducts. In combination with cholangiography, extrahepatic biliary pathology can be visualized. In cases where pathology of the arterial anastomosis is suspected, angiography can prove the patency or nonpatency of the arterial and portal circulation.

None of these procedures, however, can differentiate rejection from viral hepatitis. Even liver biopsies do not always allow this differentiation to be made. Because of this difficult differential diagnosis, immunosuppressive treatment has not always been adjusted appropriately. At times, rejections have been treated as viral infections by reducing the immunosuppressive treatment, while at other times, viral infections have been treated as rejections by increasing the immunosuppressive treatment. Furthermore, viral infections have sometimes been followed by acute rejections without a resumption of full immunosuppressive treatment in time.

How can the inappropriate adjustment of immunosuppressive treatment be prevented? So far, no reliable techniques have been available for detecting CMV in its earliest stages, because the seroconversion or rise in CMV titer occurs several weeks after the clinical presentation [11]. Van der Bij et al. [1] report a new monoclonal antibody test against immediate, early CMV antigens on peripheral blood leukocytes, which may be helpful in establishing an early diagnosis. Since a CMV-positive liver donor is the most likely source of CMV infection in the recipient [6, 11, 18], we have adopted the policy of selecting CMV-negative donors for our CMV-negative recipients.

The problems described in this chronic cholestasis group occurred in patients treated with a conventional immunosuppressive scheme, that is, without cyclosporine A. The fact that underimmunosuppression was not the only causative factor for cholestasis makes it probable that the diagnostic dilemmas mentioned can also occur in cyclo-

sporine A-treated patients. Once chronic cholestasis occurs, the prognosis becomes poor, and again, retransplantation is the only treatment option [4, 26], with a 49% 1-year survival rate [23].

In conclusion, three basic events may induce a chain of fatal complications following liver transplantation. Early recognition of these basic patterns enables one to anticipate later complications. This can help to prevent graft loss, reduce morbidity, and improve survival after liver transplantation.

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