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Surg Today (2014) 44:2293–2299
DOI 10.1007/s00595-014-0839-y

ORIGINAL ARTICLE

Impact of preoperative uncontrollable hepatic hydrothorax and massive ascites in adult liver transplantation

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Received: 23 April 2013 / Accepted: 16 December 2013 / Published online: 8 February 2014

Abstract
Purpose Uncontrollable hepatic hydrothorax and massive ascites (H&MA) requiring preoperative drainage are sometimes encountered in liver transplantation (LT). We retrospectively analyzed the characteristics of such patients and the impact of H&MA on the postoperative course.
Methods We evaluated 237 adult patients who underwent LT in our institute between April 2006 and October 2010.
Results Recipients with uncontrollable H&MA (group HA: $n = 36$) had more intraoperative bleeding, higher Child–Pugh scores, lower serum albumin concentrations and higher blood urea nitrogen concentrations than those without uncontrollable H&MA (group C: $n = 201$). They were also more likely to have preoperative hepatorenal syndrome and infections. The incidence of postoperative bacteremia was higher (55.6 vs. 46.7 %, $P = 0.008$) and the 1- and 3-year survival rates were lower (1 year: 58.9 vs. 82.9 %; 3 years: 58.9 vs. 77.7 %; $P = 0.003$) in group HA than in group C. The multivariate proportional regression analyses revealed that uncontrollable H&MA and the Child–Pugh score were independent risk factors for the postoperative prognosis.
Conclusions Postoperative infection control may be an important means of improving the outcome for patients with uncontrollable H&MA undergoing LT, and clinicians should strive to perform surgery before H&MA becomes uncontrollable.

Keywords Hepatic hydrothorax · Liver transplantation · Massive ascites · Bacteremia · Mortality

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Introduction

Liver transplantation (LT) is now performed in many countries as a treatment for end-stage liver disease. As a result of expansion of the indications for LT for HCC candidates, it also provides a potentially curative treatment for unresectable hepatocellular carcinoma, and satisfactory long-term outcomes have been achieved [1]. However, LT still has a relatively high mortality rate compared with other hepatobiliary-pancreatic procedures owing to the potentially poor preoperative condition of the patients, the use of immunosuppressive agents, and the development of rejection and infection. The preoperative condition of transplant recipients is a particularly important factor that influences the outcome of LT.

Patients requiring LT sometimes present with uncontrollable hepatic hydrothorax and massive ascites (H&MA) that must be drained before surgery; it has also been reported that H&MA is an independent risk factor for postoperative bacteremia [2].

In this study, we focused on preoperative uncontrollable H&MA in LT candidates, and evaluated the perioperative course of patients who went on to become LT recipients.

Methods

Patients

Between April 2006 and October 2010, 237 adult patients underwent LT at Kyoto University Hospital, Japan (227 were living-donor cases and 10 were deceased-donor cases). There were 117 males and 120 females; their median age was 54.9 years (range 18–69 years). The indications for LT in these patients included hepatocellular carcinoma in 78 cases; hepatocellular diseases, such as hepatitis B virus-associated liver cirrhosis, hepatitis C virus-associated liver cirrhosis and alcoholic liver cirrhosis in 133 cases; progressive intrahepatic cholestatic diseases, such as primary biliary cirrhosis and primary sclerosing cholangitis in 29 cases; re-transplantation owing to graft loss in 17 cases; fulminant hepatic failure in 17 cases; cryptogenic cirrhosis in 14 cases; biliary atresia after the Kasai operation in eight cases; autoimmune hepatitis in six cases; metabolic liver diseases in six cases and other causes in seven cases.

Antimicrobial prophylaxis

The perioperative antimicrobial prophylaxis consisted of cefotaxime (2 g/day intravenously) and ampicillin (4 g/day intravenously) twice daily for 72 h starting 30 min before surgery. Laxatives were administered as bowel preparation.

The therapeutic antibiotics were usually determined based on the results of culturing samples taken from infection sites or blood. When the focus of the infection was unknown, broad-spectrum antibiotics were administered empirically. Pre-transplant, antibiotics were given to treat ongoing infections, such as spontaneous bacterial peritonitis or pneumonia.

Immunosuppression

The standard immunosuppression protocol comprised tacrolimus and a low-dose steroid. We endeavored to maintain the whole blood trough level of tacrolimus between 10 and 15 ng/mL during the first 2 weeks, around 10 ng/mL during the next 2 weeks and between 5 and 8 ng/mL thereafter. For the recipients who suffered from side effects due to the tacrolimus treatment, we changed the immunosuppressant from tacrolimus to cyclosporine microemulsion.

Steroid therapy with methylprednisolone sodium succinate was initiated at a dose of 10 mg/kg before graft reperfusion and then tapered from 1 mg/kg/day on day 1 to 0.3 mg/kg/day by the end of the first month; this was followed by 0.1 mg/kg/day until the end of the third month. Steroid administration was terminated thereafter. In the event of postoperative infection, steroids were discontinued, and the target trough level of tacrolimus was decreased.

Study design

The medical records of patients undergoing LT were examined retrospectively to identify the recipients who had required preoperative drainage due to uncontrollable H&MA (allocated to group HA; $n = 36$) and those who had not (allocated to a control group [group C]; $n = 201$). The recipients' demographic details, surgical data, occurrence of preoperative hepatorenal syndrome (HRS) and postoperative bacteremia, and patient survival were recorded and compared between the groups. Finally, the independent prognostic factors for the patient survival were evaluated by the multivariate analyses.

Indications for thoracic or intraperitoneal drainage

We considered refractory uncontrollable massive ascites as that meeting the criteria for grade 3 with diuretic resistance, as defined by the International Ascites Club [3]. The diagnosis of hepatic hydrothorax was based on evidence of a large volume effusion (estimated to be >500 ml) on chest radiography and/or computed tomography (CT) scans in the absence of underlying pulmonary or cardiac diseases [4].

We used the following indications to guide decisions about when to drain H&MA before surgery: (1) patients with hydrothorax who remained hypoxic with a peripheral oxygen saturation (SpO_2) of ≤95 % despite supplemental oxygen administration underwent thoracic drainage to improve their respiratory function; (2) patients with hepatorenal syndrome (HRS) underwent peritoneal or thoracic drainage with intravenous albumin supplementation to normalize their hemodynamic parameters and prevent the progression of renal dysfunction and (3) patients experiencing dyspnea, difficulty eating and drinking or abdominal pain underwent thoracic or peritoneal drainage for symptomatic relief.

Hepatorenal syndrome was diagnosed according to the criteria of the International Ascites Club [5] as follows: (1) a low glomerular filtration rate, indicated by serum creatinine >1.5 mg/dl or 24-h creatinine clearance <40 ml/min; (2) the absence of shock, ongoing bacterial infections and recent or current treatment with nephrotoxic drugs; (3) no sustained improvement of renal function by diuretic withdrawal and intravenous administration of fluids and (4) the absence of significant proteinuria (<500 mg/day) and ultrasonographic abnormalities in the kidneys.

Infections and bacteremia were defined using the criteria proposed by the Centers for Disease Control and Prevention and based on our previous report regarding LT patients [2]. The diagnosis of infection in ascitic fluid or pleural effusion, including spontaneous bacterial peritonitis (SBP) and spontaneous bacterial empyema (SBEM), was based on the level of polymorphonuclear white cells (>250/mm^3 with positive culture or >500/mm^3 if culture was negative) [6, 7].

Thoracic and intraperitoneal drainage were not indicated as a treatment for SBEM and SBP in general, and antimicrobial therapy was started immediately instead of drainage. In cases where SBEM or SBP had been diagnosed after the initiation of drainage, drainage was maintained in combination with antimicrobial therapy.

The study protocol was approved by the Medical Ethics Committee of Kyoto University, and the study was performed in accordance with the ethical standards established in the 1975 Declaration of Helsinki.

Drainage protocol

We used fine catheters (Argyle^{TM} aspiration Seldinger kit, 5Fr; COVIDIEN Japan, Shizuoka, Japan) for thoracic and intraperitoneal drainage to avoid injuring collateral vessels. Before performing drainage, Doppler ultrasonography and CT were used to establish the location of any abnormal intercostal or abdominal wall collateral vessels so as to avoid hemorrhage. To prevent hypotension, depletion of protein and electrolytes, and re-expansion pulmonary edema, the rapid drainage of ascites and pleural effusion was avoided. Initially, 1,000 ml was drained, and then the drainage volume was gradually increased from the second day. At the same time, intravenous fluid and albumin replacement was undertaken during the drainage.

Statistical analysis

The values are presented as the means and standard deviations (SD) unless otherwise indicated. Continuous data were analyzed by Student's t test or the Mann–Whitney test, while categorical data were analyzed with the Chi-square test. For the survival analyses, Kaplan–Meier survival curves were constructed and analyzed by the log-rank test, and the multivariate analyses of survival were performed by the proportional regression hazard analyses. Variables identified as significant ($P < 0.05$) in the univariate analyses were considered to be candidates for the multivariate analyses. Values of $P < 0.05$ were considered to be significant. The statistical analyses were performed using the Prism version 5 software program (GraphPad Software Inc., San Diego, USA) for the univariate analyses and the JMP version 9 software program (SAS institute Inc., Cary, NC, USA) for the multivariate analyses.

Results

Details of preoperative drainage management

Preoperative thoracic or intraperitoneal drainage was performed in 36 patients (15.2 %), all of whom later underwent scheduled living-donor LT. In 16 cases, thoracic drainage was required (including five cases with SBEM), intraperitoneal drainage was performed in 15 cases (including eight cases of SBP); and both thoracic drainage and intraperitoneal drainage were needed in five cases (including two cases of SBP). The median drainage period was 13 days (range 1–33 days) for thoracic drainage and 9 days (1–44 days) for intraperitoneal drainage.

Infectious complications related to the placement of an intraperitoneal drainage tube occurred in three patients (8.3 %), while there were no complications related to the placement of a thoracic drainage tube. Infections were diagnosed 2, 6 and 7 days after the placement of the drainage catheter; patients were treated with antibiotics and a new catheter was re-sited. There were no other complications, such as hemothorax or pneumothorax.

Patient characteristics

Table 1 shows the characteristics of the groups; there were no significant differences in the sex, recipient age, blood type compatibility, graft-recipient weight ratio (GRWR), length of the operation, cold and warm ischemic times, model for end-stage liver disease (MELD) score, evidence of preoperative hepatic encephalopathy or preoperative serum creatinine of the patients in each group. Group HA was characterized by a higher intraoperative blood loss ($P = 0.02$), higher Child–Pugh score ($P = 0.001$), lower preoperative serum albumin concentration ($P = 0.01$) and higher serum blood urea nitrogen concentration ($P = 0.003$) compared with group C.

Preoperative HRS and perioperative infections

Group HA had a significantly higher incidence of HRS than group C (nine out of 36 cases [25 %] vs. 20 out of 201 cases [9.9 %], $P = 0.017$), and a significantly higher incidence of preoperative infections (19 out of 36 cases [52.8 %] vs. 35 out of 201 cases [17.4 %], $P = 0.0001$). The incidence of bacteremia within 90 days of LT was significantly higher in group HA than group C (20 out of 36 cases [55.6 %] vs. 94 out of 201 cases [46.7 %], $P = 0.008$).

Table 1 Background and characteristics of the two groups

	Group HA ($n = 36$)	Group C ($n = 201$)	P
Sex (male/female)	18/18	99/102	0.54
Age	55.3 ± 7.89	51.1 ± 12.81	0.05
ABO compatibility	Identical/compatible 28	Identical/compatible 153	0.51
	Incompatible 8	Incompatible 48	
Graft type	Right 15, left 19	Right 114, left 71	0.08
	Posterior 2	Posterior 6, whole 10	
GRWR	0.90 ± 0.17	0.98 ± 0.31	0.14
Operation time (min)	814.8 ± 120.5	793.6 ± 149.4	0.45
Blood loss (ml)	12,244.2 ± 9,505.48	8,814.4 ± 7,251.1	0.02
CIT (min)	98.1 ± 53.3	119.1 ± 113.0	0.31
WIT (min)	43.6 ± 13.2	48.6 ± 53.4	0.60
MELD score	20.9 ± 8.84	20.5 ± 9.47	0.79
Child–Pugh score	11.4 ± 2.20	10.0 ± 2.22	0.001
Preop hepatic encephalopathy	1.44 ± 0.65	1.32 ± 0.65	0.1517
Preop serum Alb (g/dl)	2.65 ± 0.42	2.94 ± 0.52	0.001
Preop serum BUN (mg/dl)	28.9 ± 19.4	18.9 ± 14.3	0.0003
Preop serum Cr (mg/dl)	1.17 ± 0.68	1.19 ± 3.58	0.98

GRWR graft-recipient weight rate, *CIT* cold ischemic time, *WIT* warm ischemic time, *MELD* model for end-stage liver disease, *Preop* preoperative, *Alb* albumin, *BUN* blood urea nitrogen, *Cr* creatinine

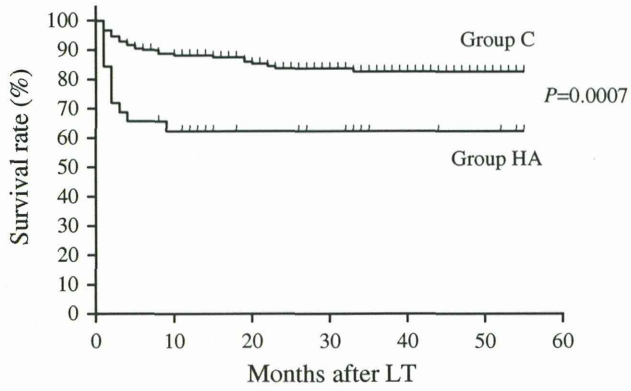

Fig. 1 The survival rates of patients with (group HA) and without (group C) uncontrollable H&MA. The cumulative survival rates after LT were significantly lower in group HA than in group C ($P = 0.0007$)

Postoperative mortality

Figure 1 shows the Kaplan–Meier survival curves of each group. The cumulative survival rates at 1 and 3 years after LT were both significantly lower in group HA than group C (1-year survival: 58.9 vs. 82.9 %; 3-year survival: 58.9 vs. 77.7 %, respectively; $P = 0.003$). The survival was worse in the HA group regardless of whether the patient had undergone intrathoracic or intraperitoneal drainage (Fig. 2a, b). Even when cases of infectious H&MA were excluded, those with sterile preoperative H&MA ($n = 23$) had a significantly worse prognosis than those in group C (1-year survival: 64.6 vs. 88.1 %; 3-year survival: 64.1 vs. 82.6 %, respectively; $P = 0.015$; Fig. 3).

When we subdivided the patients in group HA into two groups based on where there was a diagnosis of postoperative bacteremia, we found that the 1- and 3-year survival rates were significantly lower in those who developed bacteremia compared with those who did not (1-year survival: 41.2 vs. 86.2 %; 3-year survival: 41.2 vs. 86.2 %, respectively; $P = 0.008$).

Prognostic indicators after LT

The intraoperative blood loss, Child–Pugh score, preoperative albumin and blood urea nitrogen concentrations, HRS, preoperative infection and GRWR were included in the multivariate analysis, along with preoperative uncontrollable H&MA. We found that preoperative uncontrollable H&MA (hazard ratio: 2.304; $P = 0.034$) and the Child–Pugh score (hazard ratio: 1.258; $P = 0.003$) were independent risk factors for mortality after LT (Table 2).

Discussion

We analyzed the incidence and characteristics of patients with uncontrollable H&MA before LT and evaluated its effect on the postoperative course after LT.

Hepatic hydrothorax is thought to occur secondary to the passage of ascites through a diaphragmatic defect. Therefore, we included patients with hepatic hydrothorax and those with massive ascites in the same group. When we subdivided these patients into two groups based on the type of drainage, the survival rates were almost the same.

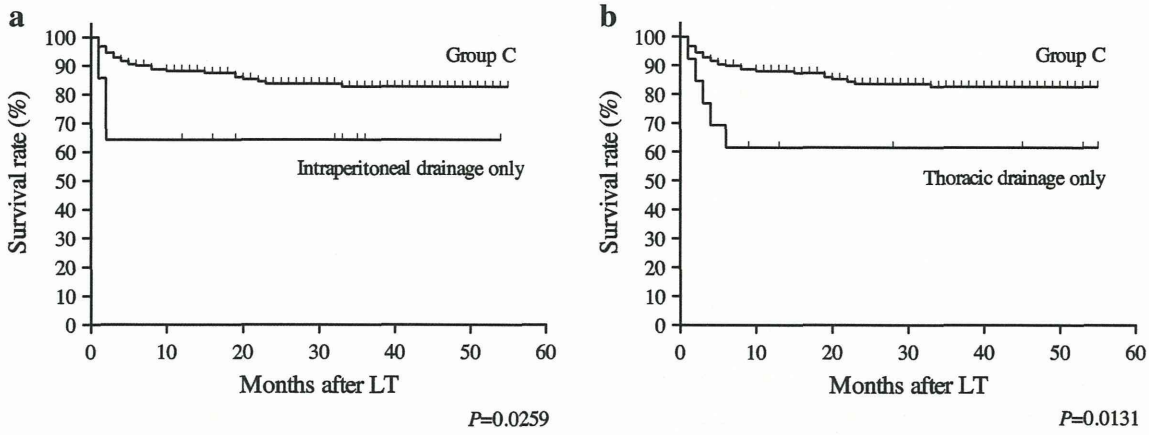

Fig. 2 The survival rates of patients depending on the site of drainage. Patients who underwent intraperitoneal drainage (**a**) and those who underwent thoracic drainage (**b**) had higher mortality rates than those in group C

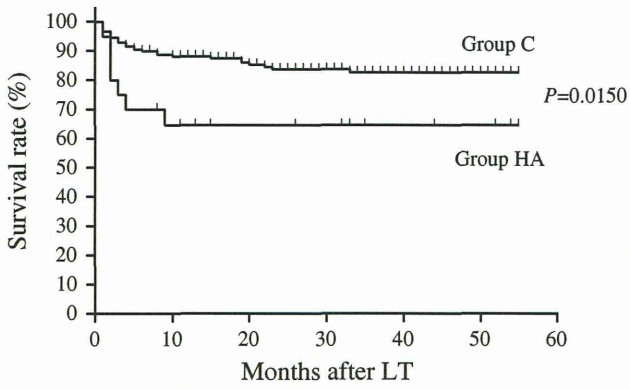

Fig. 3 Kaplan–Meier curves comparing group HA and group C after excluding the infectious H&MA cases from group HA. The mortality rates were still significantly higher in group HA than in group C

Table 2 Independent prognostic risk factors for mortality after liver transplantation

Variable	Hazard ratio	95 % Confidence interval	*P*
Preop uncontrollable hydrothorax and massive ascites	2.304	1.069–4.691	0.0339
Blood loss	1.000	0.999–1.000	0.1123
Child–Pugh score	1.258	1.085–1.422	0.0033
Preop serum Alb	1.003	0.460–2.144	0.9938
Preop serum BUN	1.004	0.983–1.024	0.7006
HRS	1.345	0.434–3.633	0.5884
Preop infection	1.088	0.493–2.270	0.8281
GRWR	0.971	0.269–3.036	0.9612

Preop preoperative, *H&MA* hydrothorax and massive ascites, *Alb* albumin, *BUN* blood urea nitrogen, *GRWR* graft-recipient weight ratio

Ascites is attributed to impaired albumin production in the liver, portal hypertension and salt retention owing to renal dysfunction. These symptoms are usually treated with a high-protein diet and diuretics, but in some cases, the ascites proves to be refractory to manipulating the dose and type of diuretics and dietary intake. A vicious cycle may develop in which increasing abdominal distension further impairs the hepatic function. Ascites and hydrothorax can cause SBP and SBEM, respectively, and can also cause a decrease in the circulating blood volume, which can lead to HRS. A transhepatic intra-jugular porto-systemic shunt (TIPS) is one of the options for treating refractory hepatic hydrothorax and massive ascites, and there are reports that TIPS is superior to large volume paracentesis in the control of ascites or hydrothorax [8, 9]. However, this treatment only provides supportive care and cannot prolong survival.

It is well recognized that the pre-transplant health of an LT recipient is closely associated with the postoperative mortality. Our study showed that patients with preoperative uncontrollable H&MA had a higher mortality rate after LT. The causes of death were mainly related to postoperative infections, including bacteremia. Notably, when cases of infectious H&MA were excluded, the remaining recipients with uncontrollable H&MA still had a poorer survival than those in group C. This finding suggests that LT recipients with uncontrollable H&MA are at risk of post-transplant mortality, regardless of the presence of preoperative infection. It is likely that the recipients in group HA were more severely compromised by more severe end-stage liver disease. The higher rate of postoperative infections in group HA might also be a consequence of the poorer general condition and comorbidities of the patients with high Child–Pugh scores. The substantially reduced survival rates in the patients in group HA diagnosed with postoperative infections suggests that effective postoperative

infection control could be a crucial means of improving the outcome after LT.

The MELD scores were not substantially different between the groups in our study. The MELD score is a useful means of prioritizing the waiting list, but it is controversial as to whether it can effectively predict the survival after LT [10–12]. The multivariate proportional hazard analyses in the present study revealed that uncontrollable H&MA was an independent risk factor for postoperative mortality. Somsouk et al. [13] reported that patients with moderate ascites and a MELD score <21 were at higher risk of death while on the waiting list for LT. It is possible that the presence of preoperative uncontrollable H&MA may be a more important prognostic indicator than the MELD scores. Clinicians should therefore carefully consider the timing of LT, undertaking transplantation before H&MA becomes uncontrollable.

Xiol et al. [14] and Serste et al. [15] have reported that the presence of preoperative hepatic hydrothorax had no significant negative influence on the postoperative outcome after deceased-donor LT. Xiol et al. [14] reported that the survival rate of patients with hydrothorax was 70 % at 8 years. However, in their hydrothorax group, they included not only patients with refractory hydrothorax, but also those with previous episodes of spontaneous bacterial empyema and those with uncomplicated hydrothorax with impaired hepatic function. In addition, the Child–Pugh score in their hydrothorax group was 9.9 ± 1.4, which was lower than that in our study (mean: 11.5). Serste et al. [15] established two control groups: a group with ascites but not hydrothorax, and a group with no ascites or hydrothorax, and compared the survival among the three groups. They found no significant differences in the overall risk of death, but the 1-year survival rate in the hydrothorax group was 64 ± 15 %, which was higher than expected. The apparent discrepancy in these findings regarding the impact of hydrothorax may also be a consequence of the type of LT. Most of the cases in the studies by Xiol and Serste [14, 15] were deceased-donor LT cases, while all of our cases received grafts from living donors. As the graft volume is limited in living-donor LT, the H&MA may have persisted due to higher portal venous pressures and hypoalbuminemia resulting from the inadequate postoperative hepatic synthetic function.

It has still not been established whether thoracic and/or intraperitoneal drainage is the best means of managing uncontrollable H&MA for liver cirrhosis (LC) before scheduled LT. However, complications related to paracentesis have been reported in only about 1 % of patients with coagulopathy [16]. Therefore, intraperitoneal drainage appears to be a safe approach. According to the treatment guidelines for LC [17, 18], intraperitoneal drainage is an effective first-line treatment for uncontrollable tense and refractory ascites. Total paracentesis reduces the intra-abdominal, intrathoracic, right arterial and pulmonary pressures, improving cardiac output by increasing the stroke volume without changing the heart rate [19]. Moreover, it results in a rapid decrease in portal pressure by decreasing the wedged hepatic venous pressure, and hence the hepatic venous pressure gradient [20]. Although intraperitoneal drainage is an established treatment for uncontrollable massive ascites, there are no data on its role in the management of SBP [18].

Regarding the management of refractory hydrothorax, thoracic drainage using a chest tube should be avoided due to the risk of complications [21]. It has been reported that chest tube insertion for hepatic hydrothorax carries significant morbidity and mortality, with questionable benefit [22, 23]. However, in our institution, the morbidity was 8.3 %, and all morbidities were related to intraperitoneal drainage. We experienced no serious or fatal complications, such as hemothorax or pneumothorax.

Drainage of H&MA might adversely influence a patient's preoperative condition. For example, the drainage of fluid could cause electrolyte and hemodynamic disturbance, and impair renal function. This can be prevented by adequate volume replacement with an appropriate combination of intravenous fluids. Nevertheless, the antibodies and immunocompetent cells in the hydrothorax and ascitic fluid cannot be replaced, which might result in a state of relative immunodeficiency, thus increasing the rate of postoperative infections.

Thoracic and intraperitoneal drainages alone without LT will not improve the prognosis of patients with end-stage liver diseases, but we should aim to improve the recipient's condition as much as possible before LT, especially if living-donor procedures are to be performed. We have recently ensured that the drainage of ascites or hydrothorax is not undertaken during the 3 days before LT in an effort to avoid intraperitoneal infections.

There are several limitations associated with our study. These are that it was a retrospective, single-center study, and the numbers of patients are small. We believe that a larger series and a multicenter study design would address these issues.

In conclusion, uncontrollable H&MA was found to be an independent risk factor for a poor post-transplant outcome in our study. In particular, for patients with uncontrollable H&MA, effective postoperative treatment of infections is a key to improving the outcome after LT. In addition, the timing of transplant is crucial; efforts should be made to perform surgery before H&MA becomes uncontrollable.

Conflict of interest The authors have no conflicts of interest to declare in association with this study.

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TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Donor morbidity in right and left hemiliver living donor liver transplantation: the impact of graft selection and surgical innovation on donor safety

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Keywords
biliary complication, hilar dissection, liver transplantation, living donor, morbidity.

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Conflicts of interest
The authors disclose no conflicts of interest.

Received: 14 October 2013
Revision requested: 29 November 2013
Accepted: 28 July 2014
Published online: 23 September 2014

doi:10.1111/tri.12414

Summary

This study investigated adequate liver graft selection for donor safety by comparing postoperative donor liver function and morbidity between the right and left hemilivers (RL and LL, respectively) of living donors. Between April 2006 and March 2012, RL (n = 168) and LL (n = 140) donor operations were performed for liver transplantation at Kyoto University Hospital. Postoperative hyperbilirubinemia and coagulopathy persisted in RL donors, whereas the liver function of LL donors normalized more rapidly. The overall complication rate of the RL donors was significantly higher than that of the LL donors (59.5% vs. 30.7%; $P < 0.001$). There were no significant differences in severe complications worse than Clavien grade IIIa or in biliary complication rates between the two donor groups. In April 2006, we introduced an innovative surgical procedure: hilar dissection preserving the blood supply to the bile duct during donor hepatectomy. Compared with our previous outcomes (1990–2006), the biliary complication rate of the RL donors decreased from 12.2% to 7.2%, and the severity of these complications was significantly lower. In conclusion, LL donors demonstrated good recovery in postoperative liver function and lower morbidity, and our surgical innovations reduced the severity of biliary complications in living donors.

Introduction

The first living donor liver transplantation (LDLT) using the left lateral segment was performed for a paediatric recipient in 1988 [1]. After the first successful case was reported in 1990 [2], LDLT in children became accepted worldwide within a few years. LDLT has emerged as an alternative method for reducing the waiting period and the mortality of patients on the waiting list [3,4]. Given the success of paediatric liver transplantation (LT) and the unavailability of deceased donor organs, Japanese LT surgeons extended the indications for LDLT to adult patients, and the first successful LDLT using a left hemiliver (LL) graft in an adult patient was performed [5]. LL grafts subsequently became common for use in adult patients.

The first LDLT using a right hemiliver (RL) graft in a child was performed at our institution [6], and because an inferior graft survival rate with smaller grafts [less than a graft-to-recipient weight ratio (GRWR) of 0.8%] was reported [7], the transplantation of RL grafts in adult patients has rapidly expanded as a standard procedure worldwide.

Donor safety is the first priority in LDLT, and among the most important complications of donor surgery are biliary complications, including bile leakage and biliary stricture. Our previous study reported that biliary complications occurred more frequently in RL donations than in LL donations and that the severity was also greater in RL donations [8]. Hence, in April 2006, we introduced a surgical procedure to avoid biliary complications in donor surgery. We also modified our graft selection criteria. We

