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Risk Factors for Intractable Ascites After Adult-to-Adult Living Donor Liver Transplantation Using Left Lobe

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Background. Intractable ascites is one of the causes of graft loss after adult-to-adult living donor liver transplantation (LDLT) using a small graft. Identification of factors associated with increasing posttransplant ascites has important implications for prevention and treatment. **Methods.** All 59 consecutive adult patients who underwent left lobe LDLT without portal inflow modulation between October 2002 and February 2016 were prospectively enrolled. Factors associated with the average daily amount of ascites for 2 weeks after LDLT were assessed. **Results.** The median daily amount of ascites during the 2 weeks was 1052 mL (range, 52-3480 mL). Although 16 of the 59 patients developed intractable ascites, exceeding 1500 mL daily (massive ascites group), the remaining 43 patients produced less than 1500 mL of ascites daily (nonmassive ascites group). The presence of pretransplant ascites ($P = 0.001$), albumin ($P = 0.011$), albumin/globulin ratio ($P = 0.026$), cold ischemia time ($P = 0.004$), operation time ($P = 0.022$), and pretransplant portal vein pressure (PVP) ($P = 0.047$) differed significantly between the 2 groups. Neither posttransplant PVP nor portal vein flow differed between the 2 groups. The variables associated with intractable ascites that remained significant after logistic regression analysis were pretransplant PVP ($P = 0.047$) and cold ischemia time ($P = 0.049$). After appropriate fluid resuscitation for intractable ascites, 58 (98%) of the 59 recipients were discharged from hospital after removal of the indwelling drains. **Conclusions.** It is important to shorten the scold ischemia time to reduce massive ascites after LDLT. Pretransplant portal hypertension is more closely associated with ascites production than posttransplant hemodynamic status.

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Small to moderate amounts of ascitic fluid are often observed in the early postoperative period after whole liver transplantation, but disappear in a few days. On the other hand, when a patient with an undersized partial graft suffers persistent portal hyperperfusion, posttransplant ascites, which is one of the elements of small-for-size syndrome (SFSS), will be prolonged.[1,2] Especially, adult-to-adult living donor liver transplantation (LDLT) using a left lobe is sometimes unable to meet the functional demands of the recipient and results in intractable ascites.[3,4] Recently, to overcome SFSS, several technical innovations, such as splenic artery ligation, splenectomy, or hemiportocaval shunt, have been implemented to modulate portal inflow to limit the negative effect of high flow in smaller grafts.[5-7] However, we have been performing left lobe LDLT with a preoperatively estimated graft volume (GV) to recipient standard liver volume (SLV) ratio (GV/SLV ratio) of 30% or greater, without either splenectomy or portocaval shunt in any of the patients and reported relatively good results.[8-10] In the present study, we explored the risk factors for intractable ascites in patients who underwent left lobe LDLT by analyzing perioperative donor and recipient characteristics.

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MATERIALS AND METHODS

Patients

Between September 2003 and February 2016, 76 consecutive LDLTs were performed at Juntendo University Hospital after

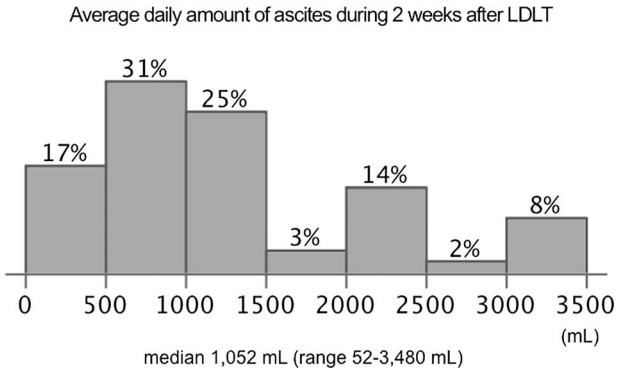

FIGURE 1. The median daily amount of ascites during 2 weeks was 1052 mL (range, 52-3480 mL).

obtaining approval from the Ethics and Indications Committee of Juntendo University. The recipients comprised 59 adults (aged ≥18 years) and 17 children (aged <18 years). All 59 consecutive adult patients who underwent left lobe-LDLT were included in the present study.

Graft Selection Criteria

We used only left lobe grafts without the caudate lobe for adult recipients and did not perform right lobe LDLT in this series. SLV of the recipients was calculated according to the formula of Urata et al.[11] GV was calculated by CT volumetric analysis, and actual GV was measured on the back table. Our general selection criteria for grafts in adult-to-adult LDLT included a preoperatively estimated GV/SLV ratio equal to or greater than 30%.[10]

Measurement of Hepatic Hemodynamics

The technique of LDLT has been previously described.[9] Intraoperative blood flow measurements were taken with an ultrasonic transit time flow meter (Transonic System, Ithaca, NY) in the recipient. After anastomosis of all the vessels and 15 minutes of equilibration, but before biliary reconstruction, hepatic artery flow and portal vein flow (PVF) were measured. The portal vein pressure (PVP) of the native diseased liver was measured before hepatectomy, and also after graft implantation, by direct puncture with a 25-gauge needle and pressure tubing attached to a normal central venous pressure (CVP) monitoring transducer. All patients underwent CVP monitoring. The portal pressure gradient was defined as the PVP minus the CVP.

Postoperative Care

The initial immunosuppressive regimen consisted of FK 506 and prednisone. Intensive anticoagulant treatment, carried out for more than 2 weeks after LDLT, included administration of low-dose low-molecular weight heparin (50 U/kg per day for 4 weeks), antithrombin III (target of 100% antithrombin activity for 2 weeks), nafamostat mesilate 0.1 mg/kg/hr for 1 week), prostaglandin E_1 (0.01 μg/kg per minute for 1 week), gabexate mesilate (1 mg/kg per hour for 1 week).

Management of Ascites

Postoperative ascitic fluid was drained through indwelling catheters. Production of ascites, removed through indwelling drains, was balanced by infusion of fresh-frozen plasma (FFP) according to the protein level in the ascites as follows: volume of ascites = A mL/h, total protein of ascites = B mg/dL, serum total protein = C mg/dL, FFP (A × B/C mL/h), and quarter or half-normal saline (A × [C – B]/C mL/h) was administered to maintain the serum protein and electrolyte level within normal range. Fundamentally, diuretics were not used for treatment of ascites.

Evaluation of Ascites

The average daily amount of ascites during the first 2 weeks was evaluated. Intractable ascites was defined as an average daily amount of ascites exceeding 1500 mL for 2 weeks after transplantation. To identify the possible factors related to the development of ascites, the following variables were analyzed: donor age and sex; pretransplant recipient variables, including age, sex, liver disease, history of ascites, model for end-stage live disease score, and Child-Pugh score and standard liver and renal function test results; graft related data including graft weight, GV/SLV ratio, and graft-recipient weight ratio; perioperative data, including cold ischemia time, red blood cell transfusion requirements, operation time; hemodynamic factors including pretransplant and posttransplant PVP, portal pressure gradient and PVF, and postoperative complications and in-hospital mortality.

TABLE 1.

Preoperative variables

Variables	Massive ascites group (n = 16)	Nonmassive ascites group (n = 43)	*P*
Donor factor			
Age, y	40 ± 11	36 ± 11	0.19
Sex			
Male	13	31	0.46
Female	4	12	
Recipient factor			
Age, y	50 ± 12	52 ± 12	0.46
Sex			
Male	8	12	0.12
Female	8	31	
Disease			
Cholestatic disease	7	13	0.21
Hepatocellular disease	9	26	
Others	0	4	
Presence of ascites			
Yes	13	15	0.001
No	3	28	
Presence of HCC			
Yes	6	15	0.85
No	10	28	
History of previous surgery			
Yes	7	21	0.73
No	9	22	
MELD score	17.6 ± 3.9	17.3 ± 0.9	0.88
Child-Pugh score	10.5 ± 0.5	9.6 ± 0.3	0.13
Platelet, /10^4 μL	6.8 ± 3.7	8.5 ± 6.1	0.30
Bilirubin, mg/dL	8.53 ± 7.71	7.28 ± 8.35	0.60
Total protein, g/dL	6.64 ± 0.69	6.81 ± 0.93	0.51
Albumin, g/dL	2.51 ± 0.43	2.92 ± 0.56	0.011
A/G ratio	0.63 ± 0.17	0.82 ± 0.32	0.026
Prothrombin time, %	58 ± 10	61 ± 20	0.49
Creatinine, mg/dL	0.70 ± 0.36	0.67 ± 0.23	0.74

MELD, model for end-stage live disease.

TABLE 2.
Perioperative variables

Variables	Massive ascites group (n = 16)	Nonmassive ascites group (n = 43)	*P*
Graft factor			
Graft weight, g	447 ± 74	417 ± 75	0.18
GV/SLV ratio, %	41.5 ± 6.2	38.3 ± 5.5	0.056
Surgical factor			
Cold ischemia time, min	104 ± 45	72 ± 34	0.004
Operative time, min	1037 ± 200	931 ± 131	0.022
Intraoperative blood loss, min	1814 ± 1835	1465 ± 2241	0.58
RBC transfusion			
Yes	8	32	0.08
No	8	11	
Platelet transfusion			
Yes	12	32	0.96
No	4	11	
Hemodynamic factor			
Pretransplant PVP, mm Hg	28.2 ± 4.9	22.3 ± 8.1	0.047
Posttransplant PVP, mm Hg	21.8 ± 4.6	21.4 ± 4.5	0.80
Posttransplant portal pressure gradient, mm Hg	13.5 ± 3.8	12.0 ± 4.9	0.32
Posttransplant PVF, mL/min per 100 g graft weight	338 ± 148	284 ± 160	0.31
Portal contribution, %	94 ± 6	89 ± 9	0.057

Statistical Analysis

Continuous variables were expressed as mean ± SD or the median with range, and statistical analysis of hemodynamic data was performed using Student *t* test. Qualitative variables were compared by χ^2 test. Variables were also compared by multivariate analysis using a logistic regression model. The variables that were ultimately used for a logistic regression analysis were chosen on the basis of clinical importance. Calculations were performed using the JMP 8.0 software package (SAS Institute Inc., NC). Differences at *P* less than 0.05 were considered to be statistically significant.

RESULTS

The median age of the patients was 55 years (range, 18-68 years). The recipient population included 20 male and 39 female subjects. The median daily amount of ascites during 2 weeks was 1052 mL (range, 52-3480 mL) (Figure 1), and 16 of the 59 patients (27%) developed intractable ascites after left lobe LDLT (massive ascites group). On the other hand, the remaining 43 patients (73%) produced 1500 mL of ascites or less daily, on average (nonmassive ascites group). The median duration of drainage tube placement was 40 days (range, 12-152 days). Preoperative factors affecting ascites are described in Table 1. There were significant differences in the presence of pretransplant ascites ($P = 0.001$), albumin ($P = 0.011$), and the albumin/globulin (A/G) ratio ($P = 0.026$) between the massive ascites and nonmassive ascites groups. Table 2 shows intraoperative factors affecting ascites. There were significant differences in cold ischemia time ($P = 0.022$), operation time ($P = 0.004$), and pretransplant PVP ($P = 0.047$). Postoperative factors affecting ascites are shown in Table 3. Postoperative complications, such as acute cellular rejection, prolonged jaundice, acute renal failure, biliary complications, vascular complications, recurrence of hepatitis C viral infection, and CMV infection did not differ significantly between the 2 groups. The variables associated with intractable ascites that remained significant after application of the logistic regression model were pretransplant PVP ($P = 0.047$) and cold ischemia time ($P = 0.049$) (Table 4). Among the 59 recipients, 58 (98%) were discharged from hospital. The remaining patient died 38 days after LDLT secondary to massive bleeding at the site of hepatic artery anastomosis. The overall 1-, 3-, and 5-year patient and graft survival rates were 98%, 96%, and 94%, respectively.

DISCUSSION

Ascites is a common complication after adult LDLT. The smaller left lobe graft carries an especially high risk for development of massive ascites. However, few have assessed factors associated with ascites after LDLT using the left lobe. In the present study, univariate analysis showed that pretransplant factors, such as the presence of pretransplant ascites, Child-Pugh score, albumin level, and A/G ratio, were associated with an increase in the daily amount of ascites produced after LDLT. Pretransplant PVP was the only independent risk factor for an increase in the production of ascites. In patients with severe portal hypertension, an increase in portal lymph flow occurs.[12,13] New lymphatic vessels are formed in the presence of cirrhosis, and this may accommodate increased

TABLE 3.
Postoperative variables

Variables	Massive ascites group (n = 16)	Nonmassive ascites group (n = 43)	*P*
Acute cellular rejection			
Yes	4	8	0.59
No	12	35	
Reoperation			
Yes	3	6	0.65
No	13	37	
Prolonged jaundice			
Yes	0	3	0.082
No	16	40	
Acute renal failure			
Yes	2	3	0.51
No	14	40	
Biliary complication			
Yes	1	5	0.53
No	15	38	
Vascular complication			
Yes	1	2	0.81
No	15	41	
Recurrence of hepatitis C			
Yes	3	9	0.85
No	13	34	
CMV infection			
Yes	7	22	0.61
No	9	21	
In hospital mortality			
Yes	0	1	0.42
No	16	42	
Hospital stay, d	105 ± 58	83 ± 69	0.25

TABLE 4.

Final model: factors associated with intractable ascites by logistic regression analysis

Factor	Parameter estimate	Standard error	95% Confidence interval	*P*
Operation time, min	–0.005	0.007	–0.020 to 0.009	0.51
Cold ischemia time, min	0.074	0.038	0.012-0.167	0.049
GV/SLV ratio, %	–0.073	0.120	–0.331 to 0.160	0.54
Pretransplant PVP, mm Hg	0.197	0.099	0.026-0.429	0.047
Posttransplant PVP, mm Hg	0.061	0.132	–0.202 to 0.340	0.65

lymphatic flow. This markedly developed lymphatic drainage system is destroyed upon surgical removal of the whole liver in recipient, and a massive amount of lymphatic fluid finally flows into the peritoneal cavity.

Posttransplant ascites is more common in LDLT than in cadaveric donor liver transplantation. Cirera et al[14] reported a 7% incidence of ascites after whole-liver transplantation, although their definition of intractable ascites was slightly different.

Our study showed that intractable ascites developed in 31 patients (53%) after left lobe LDLT. Contrary to the widely held clinical impression, the average daily amount of ascites was not correlated with the GV/SLV ratio. Although the incidence of intractable ascites after right-lobe LDLT has been reported to be 23.7%[15] or 25.7%,[16] Ikegami et al[17] reported relatively low incidence of massive ascites, which was recognized in only 15 (12.5%) of 120 left-lobe LDLT recipients. The outflow of a left lobe graft is considered superior to that of a right lobe graft without the middle hepatic vein. Compliance per unit per liver graft weight in left lobe grafts is better than that in right lobe grafts without the middle hepatic vein.[18] Thus, in patients undergoing LDLT, the size of the graft itself may not be an important factor determining the risk for posttransplant intractable ascites.

Although various techniques for graft inflow modulation have been reported to eliminate the issue of SFSS,[5-7] we have performed left lobe LDLT without portal inflow modulation. The development of ascites seems to require a minimal portal pressure gradient of 10 mm Hg and a portal pressure gradient of 10 mm Hg or more has been defined as "clinically significant portal hypertension" because complications do not occur below this threshold pressure.[19] In the present study, 38 (79%) of 48 recipients had a portal pressure gradient exceeding 10 mm Hg. The high incidence of intractable ascites in the present series may be related to the high portal pressure gradient after LDLT.

In the present study, a longer operation time and a longer cold ischemia time were significantly related to an increase in ascites production. A prolonged cold ischemia time leads to postoperative damage to liver function, and more serious liver dysfunction will lead to much greater postoperative ascites production.[16] Although transient posttransplant liver dysfunction was recognized just after LDLT, most of the recipients' posttransplant courses were characterized by immediate recovery of graft function, with steady normalization of serum total bilirubin and clotting profiles. The amount of ascites gradually decreased in accordance with improvement of liver function.

Appropriate management of ascites is required. The amount of urine can be varied to maintain whole-body fluid homeostasis. This is achieved via many homeostatic regulatory mechanisms that change the amount of water and solutes in urine. On the other hand, ascites is discharged without any autoregulation. The amount of ascites should be recorded hourly and replaced with an equal volume of FFP combined with crystalloid. The proportion of FFP to crystalloid is calculated from the total protein levels in ascites and serum. Although rapid regeneration is observed in left lobe recipients because of high liver blood flow after LDLT, it takes a long time for liver function to recover because the early phase of regeneration is mainly associated with vascular engorgement and tissue edema.[20] Such precise fluid replacement therapy should be continued until the liver graft recovers its proper function. Thereafter, drained ascitic fluid gradually decreases and the tubes can finally be removed. Portal hyperperfusion is improved at 1 or 2 months after LDLT. It is important to overcome the posttransplant acute phase through meticulous management.

In conclusion, shortening of the cold ischemia time and operation time, and appropriate fluid resuscitation are important for the management of intractable posttransplant ascites. Analysis of the present results suggests that preoperative portal hypertension is a more crucial factor than posttransplant PVP or PVF for increased ascites production after left lobe LDLT.

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