Acta Med. Nagasaki 47 : 127−131

Analysis of Hepatic Arterial Thrombosis after Liver Transplantation: An Experience at a Single Transplantation Center

Atsushi NANASHIMA

First Department of Surgery, Nagasaki University School of Medicine

The author has experienced to practice the clinical works of cadaveric liver transplantation at a single transplantation center in Australia between 1999 and 2000. Hepatic arterial thrombosis causes higher rates of morbidity and mortality after liver transplantation. To know the associated factors, pathogenesis and patient outcome, data of 99 adult patients who underwent liver transplantation by the database for past two years were analysed. Ten patients (10%) had hepatic arterial thrombosis (HAT group). In donor demographics, brain death caused by cerebral stroke in the HAT group (90%) was significantly more than that in the non HAT group (49%) ($p<0.05$). The mean amount of blood transfusion in the HAT group (26665ml) was significantly greater than that in the control group (15606ml) ($p<0.05$). The mean hepatic arterial flow measured by Doppler flowmeter in the HAT group (214ml/min.) was lower than that in the control group (399ml/min) ($p<0.01$). The rate of in-hospital death or retransplantation caused by severely biliary abscess with hepatic infarction or graft failure in the HAT group (40%) tended to be higher compared to the control group (13%) ($p=0.053$). In conclusion, decrease of bleeding and blood transfusion, and obtaining the adequate arterial blood flow during operation were important to prevent hepatic arterial thrombosis causing higher morbidity and mortality after liver transplantation.

ACTA MEDICA NAGASAKIENSIA 47 : 127−131, 2002

Key Words: hepatic artery thrombosis, arterial flow, blood transfusion, orthotopic liver transplantation

Introduction

In orthotopic liver transplantation (OLTx), anastomosed vascular complications in the allograft are a major complication. Particularly, hepatic arterial thrombosis (HAT) is a severe complication, which causes higher rates of graft loss, and mortality.[1-3] Early diagnosis and urgent salvage therapy such as thrombectomy, revascularization or retransplantation are necessary.[4-6] Despite technical developments in the operative procedures, HAT is still a major complication after OLTx.[1]

The author had an opportunity to train at an Australian liver transplantation center between 1999 and 2000. This was a report of a retrospective analysis of associated factors with the development of HAT and patient prognosis.

Address Correspondence: Atsushi Nanashima, M.D.
First Department of Surgery, Nagasaki University School of Medicine, 1-7-1 Sakamoto, Nagasaki, 852-8501, Japan
TEL: +81-95-849-7304 FAX: +81-95-849-7306
E-mail: a-nanasm@alpha.med.nagasaki-u.ac.jp

Patients and Methods

Patients

The study group consisted of 99 adult patients with end-stage liver disease who underwent OLTx in the Australian liver transplantation center between January 1998 and September 2000. There were 69 males and 30 females with a mean age of 46 ± 13 years (range, 17-67 years). The patients were divided into two groups as follows: 10 (10%) patients with hepatic arterial thrombosis (HAT) (the HAT group) and 89 (90%) control patients (the non-HAT group). The donor and recipient background and anesthetic records in each group were retrieved from patient charts and the database of the institute.

Characteristics of donor and recipient, operation records and post-operative parameters

Donor-associated factors were age, time ventilated in the intensive care unit, cause of brain death, evidence of resuscitation, use of inotropes, and steatosis score of donor liver. Recipient associated factors were age, cause of end stage liver disease, and Child-Turcott-Pugh (CTP) score. The preoperative status of recipients at the time of OLTx was recorded according to the grading used by this institute: Status 1-stable at home; Status 2-requiring frequent admission; Status 3-

unwell in hospital; Status 4-in ICU/ventilator dependent.

An experienced liver pathologist scored the steatosis level on pre-implantation allograft biopsy specimens. The scale of macrovesicular fat infiltration as defined at our institution is as follows; S0: absent, SI: mild, focal steatosis (<30%), SII : moderate, zone 2-3 steatosis (30-60%), SIII; severe, panlobular steatosis (>60%).[7] Operative data analyzed included operation time, total and warm ischemic times, recorded blood loss and blood transfusion, prevalence of post-revascularization syndrome (defined as a mean arterial pressure of less than 60 mmHg within 5 minutes of allograft reperfusion),[8] and flow of portal vein and hepatic artery after anastomosis. Post-operative complications including the incidence of acute rejection, sepsis, biliary complications and initially poor graft function, and early patient survival were all examined.

Surgical procedures and examined items

During the donor hepatectomy, a "no touch" technique for multiple organ retrieval was used,[9] and the allograft was preserved with cold University of Wisconsin solution. During the implantation, a veno-venous bypass was used routinely during the anhepatic period.[9] The recipient hepatectomy and implantation of the donor liver were performed according to the techniques as previously described.[9-10]

Experienced surgeons, who often used a magnifying glass, performed the vascular anastomosis. The hepatic artery of the donor liver was anastomosed at the trunk of the common hepatic artery of the recipient with 7-0 prolene, and 4-0 and 6-0 prolene were used for anastomosis of the hepatic vein and portal vein, respectively. After anastomosis of the vessels and revascularization, portal venous and hepatic arterial flow rates were measured using an ultrasonic transit-time volume flow meter (Transonic® Medical Volume Flowmeters HT207 series, Transonic Systems Inc., Ithaca, NY, USA) with the appropriate probe for the size of the vessels. Measurement of these vascular flow was performed at immediately after revascularization and after biliary anastomosis.

Statistical analysis

Data are expressed as mean ± SD. The chi-square test was used to compare differences in ratios. Data between two groups was compared using one-way analysis of variance (ANOVA) and examined by Student's t-test. A two-tailed P value < 0.05 was considered significant. The StatView Software for Windows, Version 5.0 (SAS Institute, Inc., Cary, NC) was used for all statistical analyses.

Results

In 10 HAT patients, HAT occurred in 6 patients between 2 weeks and one month and in 4 after one month after OLTx. The donor and recipient demographics are shown in Table1. In the donors, brain death by cerebral stroke in the HAT group was sig-

Table 1. Donor and recipient demographics data

		HAT group (n=10)	Control group (n=89)	p value
Donor	Age Mean (years)	50±12 (20-65) [g]	46±13 (17-67)	0.409
	>50 y.o	5 (50) [f]	32 (36)	0.764
	Ventilation time at ICU (hours)	61±46	47±38	0.363
	Allograft steatosis [a]			
	0	7 (70)	69 (78)	
	1	1 (10)	13 (15)	0.518
	2	1 (10)	2 (2)	
	3	1 (10)	5 (5)	
	Use of inotropes			
	No	1 (12)	11 (12)	0.982
	Yes	9 (88)	78 (88)	
	Cause of brain death			
	Cerebral stroke	9 (90)	44 (49)	0.049
	Trauma	1 (10)	36 (40)	
	Other	0 (0)	9 (11)	
Recipient	Age mean (years)	42±18(23-58)	43±14 (10-74)	0.824
	>50 y.o	4 (40)	29 (33)	0.916
	Cause of liver disease			
	Chronic viral hepatitis	6 (60)	33 (37)	0.186
	Non-viral hepatitis	4 (40)	56 (63)	
	Alcoholic	2 (20)	16 (18)	
	PSC [b] and PBC [c]	0 (0)	11 (12)	
	Fulminant failure	1 (10)	7 (8)	
	Retransplantation	0 (0)	7 (8)	
	Other	1 (10)	15 (17)	
	CTP [d] classification			
	A	2 (20)	16 (18)	0.987
	B	5 (50)	42 (47)	
	C	3 (30)	31 (35)	
	Clinical status [e]			
	1	4 (40)	52 (58)	
	2	5 (50)	25 (28)	0.276
	3	1 (10)	6 (7)	
	4	0 (0)	6 (7)	

a) Scale of steatosis, 0:absent, 1: mild, 2 : moderate, 3: severe (16)
b) Primary sclerosing cholangitis,
c) Primary biliary cirrhosis,
d) Child-Turcott-Pugh,
e) Status 1-stable at home; 2-frequent hospitalization; 3-hospitalized; 4-ICU
f) ( ); percentage. The chi-square test was used to compare differences in ratios.
g) Data between two groups was compared using one-way analysis of variance (ANOVA) and examined by Student's *t*-test.

nificantly more than that in the non HAT group. Patients with chronic viral hepatitis tended to be more in the HAT group compared to the non HAT group but not significant. There was a trend for recipients in the HAT group to have a lower CTP score and to be of clinical status 1. Table 2 shows data obtained from the anesthetic and surgical records during OLTx. The major significant differences were more amount of blood transfusion and lower flow rate of the artery (<250ml/minutes) in the HAT group compared to the non HAT group. There were no significant differences of mean arterial blood pressure and levels of hematocrit and international normalized ratio between the HAT group and the non-HAT group during operation (data not shown).

Table 2. Anesthetic and surgical record data during OLTx

	HAT group (n=10)	Control group (n=89)	p value
Total operation time (min.)	553±105	521±119	0.412
Anhepatic time (min.)	130±40	112±43	0.196
Total ischemic time (min.)	601±71	562±139	0.408
Warm ischemic time (min.)	51±12	52±20	0.815
Blood loss (ml)	17846±9059	11363±17815	0.395
Blood transfusion (ml)	26665±23923	15606±10701	0.010
Flow rate (ml/min.) [a]			
Portal vein	2277±795	2356±1001	0.821
Hepatic artery	214±102	399±197	0.007
(<250ml/nin.)	6 (60)	20 (23)	0.019
PRS [b]			
No	6 (60)	64 (72)	0.433
Yes	4 (40)	25 (28)	

a) Blood flow rate after anastomosis, b) Post-revascularization syndrome (mean arterial pressure <60mmHg within 5 minutes after revascularization)
P value by Student's t-test. Data are mean ± SD
( ): percentage. The chi-square test was used to compare differences in ratios.

Table 3 details the post-operative complications and patient outcome. In the present study, 83 patients (84%) were alive at 6 months after OLTx and two of these patients underwent rescue retransplantation within one month after the first OLTx. Fourteen patients (14%) were dead within 6 months after OLTx. There was a tendency for biliary complications, and the incidences of retransplantation or post-operative death, to be more frequent in the HAT group compared to the non HAT group, but there were not significant. Table 4 shows the causes of death in the HAT and the non HAT group. Three patients in the HAT group progressed to death by severe sepsis resulting from the biliary ischemia and irreversible abscess formation. One patient died from progressive

Table 3. Postoperative complications and patient survival

	HAT group (n=10)	Control group (n=89)	p value
Acute rejection			
No	5 (50)	42 (47)	1.000
Yes	5 (50)	47 (53)	
Sepsis			
No	4 (40)	52 (58)	0.481
Yes	6 (60)	37 (42)	
Biliary complications			
No	5 (50)	62 (70)	0.285
Yes	5 (50)	27 (30)	
Initially poor graft function [a]			
No	7 (70)	72 (81)	0.418
Yes	3 (30)	17 (19)	
Survival [b]			
Alive	6 (60)	77 (87)	0.053
Alive by retransplantation	2 (20)	0 (0)	
Dead	2 (20)	12 (13)	

a) Defined as an increased level of AST and/or ALT of greater than 1500 IU/l on two consecutive measurements within the first 72 hours after OLTx
b) Early prognosis within 6 months after OLTx
( ); percentage. The chi-square test was used to compare differences in ratios.

Table 4. Cause of death or retransplantation

HAT group (n=4)	Control group (n=12)
Biliary abscess with infarction 3 Graft failure 1	Sepsis 4 Primary non-functioning 3 Intraabdominal bleeding 2 Delayed graft failure 1 Graft versus host disease 1 Renal failure 1

graft failure due to liver ischemia in the HAT group. In the non HAT group, four patients died from bacterial sepsis unrelated to biliary complications such as abscess.

Discussion

The incidence of HAT complications after OLTx ranges between 2.7-10%[1,5,11-15] and is more frequent than complications of portal vein and caval anastomosis despite development of the current techniques of vascular anastomosis. In the present series, despite the small numbers of patients, HAT occurred in 10 cases, coincident with the incidence described above although the hepatic arterial anastomoses were carefully performed and checked during and after operation in each case. HAT often occurs at a late phase such as more than 30 days after OLTx, and not only in the early period.[1,12] Factors other than technical problems associated with HAT after OLTx have been reported including arterial anastomosis to conduits,[12,17]

the amount of blood transfusion,[13,19] recipient/donor weight ratio,[12,16,17] acute rejection,[12] cytomegalovirus status,[12,16] female donor to male recipient,[12] long surgical time,[17] clotting abnormalities such as anticardiolipin antibody,[20] cross matching,[18] and ABO incompatibility.[19] These factors seemed to be differently associated with thrombosis in patients between early and late HAT.[12] In the present study, the brain death by the cerebral stroke was frequent in the HAT patients. The author speculates that patients who died of the cerebral stroke might have a potential of thrombosis or hypercoagulation in the general organs. Furthermore, old donors tended to be more in the HAT patients (not significant) and such patients might have sclerotic vessels. In the recipients, the incidence of chronic viral hepatitis in the HAT group tended to be more (not significant). Oh et al. reported the association between HAT and recipient with hepatitis C-related liver disease by the multivariate analysis.[12] In the anesthetic and surgical records, the amount of bleeding during operation tended to be more in the HAT group and the increased blood transfusion of red cells was significantly associated with HAT. Abou Ella et al. and Hatano et al. also reported that increased transfusion during the transplant procedure was independently associated with an increased incidence of HAT.[13,19] Particularly, Hatano et al. stressed that overtransfusion of fresh-frozen plasma might be a critical factor in the development of HAT in living related liver transplantation.[19] In the present study, fresh frozen plasma has been used as much as red cell transfusion and, therefore, this factor may be one of causes of HAT. Surgical stress due to major operations usually leads to hypercoagulation[21] and, furthermore, an increase of hematocrit by larger amount of blood transfusions may promote abnormal clotting. We speculate that increased hyperviscosity due to overtransfusion might be a cause of occurrence of HAT by our results. Nevertheless the mean arterial blood pressure was similar between groups, the lower flow rate of hepatic artery after anastomosis, which was routinely measured using doppler ultrasonography during operation, was significantly associated with the HAT complication in the present study. In the present study, it might be thought that causes of low flow rate were hyperviscosity by the rapid blood transfusion, arteriosclerosis due to old donor, injury during organ donation, or stenosis of the anastomosed artery. In cases where the flow rate was less than 100 ml/min, the arterial anastomosis was started over again. Although a flow rate of more than 250 ml/min was thought to be adequate in our institution, Abbasoglu et al. reported that patients with a hepatic artery flow less than 400 ml/min were more than 5 times as likely to develop the hepatic artery complications.[22] The lower flow rate of the hepatic artery might be one of the factors associated with HAT. For post-operative screening of HAT after OLTx, duplex doppler ultrasonography is handy and reliable in the ward.[1,6,14,23,24]

HAT complication often leads to severe complications such as liver infarction, biliary stenosis or abscess, systemic sepsis and hepatic failure,[1-3,15] and, therefore, the mortality rate is higher[1] as seen in the results of the present series. In the present study, although the incidences of biliary complications and poor graft function in the HAT group were not significantly higher, biliary sepsis due to abscess and the graft failure caused by liver ischemia were the main causes in the patients who died or underwent retransplantation in the HAT group. Therefore, early detection and urgent treatment for HAT are very important to avoid such severe complications. Prophylactic anticoagulation therapy is proposed to avoid HAT immediately after OLTx in some institutes.[6,13] However, the application of this therapy is still controversial because of the risk of post-operative bleeding. No patient in the present study had prophylactic anticoagulant therapy after operation.

To perform urgent revascularization in patients with HAT, thrombectomy, thrombolysis and reanastomosis using another conduit are usually selected.[4-6,11,25,26] Among the 10 cases of the present study, no patient underwent the rescue therapy of thrombectomy or reanastomosis because HAT had occurred in the late phase after OLTx in these patients. Frequent routine checks of arterial flow by ultrasonography or computed tomography had been accomplished in all patients who underwent OLTx at this institute.

In living donor liver transplantation in Japan, the microsurgical technique under microscope is usually applied for reconstruction of the hepatic artery. Kawasaki et al. recently reported that the incidence of HAT had remarkably reduced as a result of the use of microsurgery.[27] To resolve the technical problem, microsurgery is the better choice for liver transplantation as well.[28] Clarifying other thrombotic factors associated with HAT is also important to reduce this complication.

In conclusion, increased blood transfusion followed by bleeding during operation was significantly associated with HAT after OLTx. In patients with HAT, the flow rate of the hepatic artery was significantly lower compared to that in non-HAT group and the incidence of HAT was greater in patients with an arterial flow less than 250 ml/minute. Biliary abscess due to

hepatic infarction occurred in 3 patients with HAT, and the incidence of mortality or re-transplantation in the HAT group was significantly higher. Reduction of bleeding and blood transfusion, and obtaining an adequate arterial blood flow during operation are important in order to avoid hepatic arterial thrombosis after OLTx.

References

1) Proposito D, Loinaz Segurola C, Garcia Garcia I, Jimenez C, Gonzalez Pinto I, Gomez Sanz R, Urruzuno P, Medina E, Moreno Gonzalez E: Diagnosis and treatment of hepatic artery thrombosis after liver transplantation. (in Italian with English abstract) *Chir Ital* 52:505-525, 2000
2) Margarit C, Hidalgo E, Lazaro JL, Murio E, Charco R, Balsells J: Biliary complications secondary to late hepatic artery thrombosis in adult liver transplant patients. *Transpl Int* 11 Suppl 1:S251-254, 1998
3) Rasmussen A, Hjortrup A, Kirkegaard P: Intraoperative measurement of graft blood flow--a necessity in liver transplantation. *Transpl Int* 10:74-77, 1997
4) Rogers J, Chavin KD, Kratz JM, Mohamed HK, Lin A, Baillie GM, Shafizadeh SF, Baliga PK: Use of autologous radial artery for revascularization of hepatic artery thrombosis after orthotopic liver transplantation: case report and review of indications and options for urgent hepatic artery reconstruction. *Liver Transpl* 7:913-917, 2001
5) Settmacher U, Stange B, Haase R, Heise M, Steinmuller T, Bechstein WO, Neuhaus P: Arterial complications after liver transplantation. *Transpl Int* 13:372-378, 2000
6) Sakamoto Y, Harihara Y, Nakatsuka T, Kawarasaki H, Takayama T, Kubota K, Kimura W, Kita Y, Tanaka H, Ito M, Hashizume K, Makuuchi M: Rescue of liver grafts from hepatic artery occlusion in living-related liver transplantation. *Br J Surg* 86:886-889, 1999
7) Chui AKK, Haghighi K, Painter D, Jayasundera M, Hall G, Rao ARN: Donor fatty (steatotic) liver allografts in orthotopic liver transplantation. *Transplant Proc* 30:3286-3287, 1998
8) Marino IR, De Luca G: Orthotopic liver transplantation in pigs. An evaluation of different methods of avoiding the revascularization syndrome. *Transplantation* 40:494-498, 1985
9) Sheil AGR, Thompson JF, Stephen MS, Graham JC, Eyers AA, Bookallil M: Liver graft revascularization by donor portal vein arterialization following "no touch" donor hepatectomy. *HPB Surg* 1:57-66, 1988
10) Starzl TE, Koep LJ, Weil R 3rd, Halgrimson CG: Development of a suprahepatic recipient vena cava cuff for liver transplantation. *Surg Gynecol Obstet* 149:77, 1979
11) Abou El-Ella K, Al Sebayel M, Ramirez C, Hussien R: Outcome and risk factors of hepatic artery thrombosis after orthotopic liver transplantation in adults. *Transplant Proc* 33:2712-2713, 2001
12) Oh CK, Pelletier SJ, Sawyer RG, Dacus AR, McCullough CS, Pruett TL, Sanfey HA: Uni- and multi-variate analysis of risk factors for early and late hepatic artery thrombosis after liver transplantation. *Transplantation* 71:767-772, 2001
13) Abou Ella KA, Al Sebayel MI, Ramirez CB, Rabea HM: Hepatic artery thrombosis after orthotopic liver transplantation. *Saudi Med J* 22:211-214, 2001
14) Cavallari A, Vivarelli M, Bellusci R, Jovine E, Mazziotti A, Rossi C: Treatment of vascular complications following liver transplantation: multidisciplinary approach. *Hepatogastroenterology* 48:179-183, 2001
15) Rabkin JM, Orloff SL, Corless CL, Benner KG, Flora KD, Rosen HR, Keller FS, Barton RE, Lakin PC, Petersen BD, Saxon RR, Olyaei AJ: Hepatic allograft abscess with hepatic arterial thrombosis. *Am J Surg* 175:354-359, 1998
16) Pastacaldi S, Teixeira R, Montalto P, Rolles K, Burroughs AK: Hepatic artery thrombosis after orthotopic liver transplantation: a review of nonsurgical causes. *Liver Transpl* 7:75-81, 2001
17) Sieders E, Peeters PM, TenVergert EM, de Jong KP, Porte RJ, Zwaveling JH, Bijleveld CM, Slooff MJ: Early vascular complications after pediatric liver transplantation. *Liver Transpl* 6:326-332, 2000
18) Sawyer RG, Pelletier SJ, Spencer CE, Pruett TL, Isaacs RB: Increased late hepatic artery thrombosis rate and decreased graft survival after liver transplants with zero cross-reactive group mismatches. *Liver Transpl* 6:229-236, 2000
19) Hatano E, Terajima H, Yabe S, Asonuma K, Egawa H, Kiuchi T, Uemoto S, Inomata Y, Tanaka K, Yamaoka Y: Hepatic artery thrombosis in living related liver transplantation. *Transplantation* 64:1443-1446, 1997
20) Pascual M, Thadhani R, Laposata M, Williams WW, Farrell ML, Johnson SM, Tolkoff-Rubin N, Cosimi AB: Anticardiolipin antibodies and hepatic artery thrombosis after liver transplantation. *Transplantation* 64:1361-1364, 1997
21) Tsuji K, Eguchi Y, Kodama M: Postoperative hypercoagulable state followed by hyperfirinolysis related to wound healing after hepatic resection. *J Am Coll Surg* 183:230-238, 1996
22) Abbasoglu O, Levy MF, Testa G, Obiekwe S, Brkic BS, Jennings LW, Goldstein RM, Husberg BS, Gonwa TA, Klintmalm GB: Does intraoperative hepatic artery flow predict arterial complications after liver transplantation? *Transplantation* 66:598-601, 1998
23) Pastacaldi S, Teixeira R, Montalto P, Rolles K, Burroughs AK: Hepatic artery thrombosis after orthotopic liver transplantation: a review of nonsurgical causes. *Liver Transpl* 7:75-81, 2001
24) Roberts JP, Hughes L, Goldstone J, Ascher NL: Examination of vascular anastomoses during liver transplantation by intraoperative Doppler duplex scanning. *Clin Transplant* 4:206-209, 1990
25) Settmacher U, Stange B, Haase R, Heise M, Steinmuller T, Bechstein WO, Neuhaus P: Arterial complications after liver transplantation. *Transpl Int* 13:372-378, 2000
26) Maguire D, Hart R, Heaton N, Rela M. A complication of infrarenal arterial conduit following orthotopic liver transplant. *HPB*; 3:275-277, 2001
27) Hashikura Y, Kawasaki S, Terada M, Ikegami T, Nakazawa Y, Urata K, Chisuwa H, Mita A, Ohno Y, Miyagawa S: Long-term results of living-related donor liver graft transplantation: A single-center analysis of 110 transplants. *Transplantation* 72:95-99, 2001
28) Furuta S, Ikegami T, Nakazawa Y, Hashikura Y, Matsunami H, Kawasaki S, Makuuchi M: Hepatic artery reconstruction in living donor liver transplantation from the microsurgeon's point of view. *Liver Transpl Surg* 3:388-393, 1997