

ORIGINAL ARTICLE

Outcome of partial reconstruction of multiple hepatic arteries in pediatric living donor liver transplantation using left liver grafts

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SUMMARY

Partial liver grafts used in living donor liver transplantation (LDLT) may have multiple hepatic artery (HA) stumps. This study was designed to validate the safety of partial reconstruction of multiple HAs in pediatric LDLT cases. From January 2000 to June 2014, 136 pediatric LDLT recipients were categorized into three groups: single HA group (Group 1, $n = 74$), multiple HAs with total reconstruction group (Group 2, $n = 23$), and multiple HAs with partial reconstruction group (Group 3, $n = 39$). Partial reconstruction was performed only when there was pulsatile back-bleeding after larger HA reconstruction and sufficient intrahepatic arterial flow was confirmed by Doppler ultrasound (DUS). There was no significant difference in biliary complication rate, artery complication rate, patient survival, and graft survival among these groups. Risk factor analysis revealed that the presence of multiple HAs and partial reconstruction of multiple HAs were not risk factors of biliary anastomosis stricture. In conclusion, partial reconstruction of HAs during pediatric LDLT using a left liver graft with multiple HA stumps does not increase the risk of biliary anastomosis stricture or affect graft survival when intrahepatic arterial communication is confirmed by pulsatile back-bleeding and DUS.

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Key words

bile duct complication, hepatic artery complication, multiple artery, pediatric liver transplantation

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Introduction

Liver transplantation (LT) has become the treatment of choice for pediatric end-stage liver disease patients [1]. However, a shortage of size-matched liver allografts in deceased donors and high mortality on the waiting list has led to the use of partial liver grafts from adult living donors [2]. Approximately 30–40% of left liver grafts and 5% of right lobe grafts have multiple arteries, and the hepatic artery (HA) is usually smaller in liver grafts with multiple HAs [3–5].

The application of microscope and surgical loupes with high magnification ($\times 3.5$ – 4.5) to HA reconstruction in living donor liver transplantation (LDLT) has significantly reduced the incidence of HAT and has improved graft survival [5–7]. In addition, several strategies have been introduced to manage liver grafts with multiple HAs [8–10]. Even with these technical advancements, whether to reconstruct all HA stumps on a graft is an ongoing debate. The points of contention include biliary complication rate and hepatic arterial complication rate. Some groups insist that partial

reconstruction of multiple HAs does not increase the biliary complication rate and possibly decreases hepatic artery complications [3,11,12]. However, other studies have demonstrated that all HAs need to be reconstructed to decrease the risk of biliary anastomotic stricture (BAS) [9,13–15].

Studies on the partial reconstruction of multiple HAs were mostly conducted with adult LDLT cases. The purpose of this study was to validate the safety of partial reconstruction of multiple HAs in pediatric LDLT cases by comparing biliary complication rates, hepatic artery complication rates, patient survival rates, and graft survival rates with those of total reconstruction cases and single artery cases.

Methods

Patients

From January 2000 to June 2014, 159 pediatric patients (recipient age ≤ 18 years) underwent LDLT at Samsung Medical Center (Seoul, Korea). Among these cases, ABO incompatible LT cases ($n = 2$), a re-transplantation case ($n = 1$), right lobe graft cases ($n = 12$), foreign patients whose regular follow-up was impossible ($n = 2$), and patients with inadequate information about hepatic artery reconstruction ($n = 6$) were excluded. The remaining 136 patients were subjects of this study and were divided into three groups: single HA (Group 1, $n = 74$), multiple HAs with total reconstruction (Group 2, $n = 23$), and multiple HAs with partial reconstruction (Group 3, $n = 39$). Partial reconstruction was defined as the presence of one or more HAs that were not anastomosed at the end of the procedure. The medical records of 136 patients were retrospectively reviewed for data on donor demographics, recipient demographics, surgical procedures, and post-operative outcomes including biliary complication and hepatic artery complication rates. The median follow-up period was 88 months (range 1–182 months).

This study protocol was reviewed and approved by the institutional review board of Samsung Medical Center, Sungkyunkwan University School of Medicine (IRB No. SMC 2015-08-029-001).

Hepatic artery reconstruction

The detailed surgical procedure for HA reconstruction is described elsewhere [16]. The HA anastomosis was fashioned with the use of an interrupted 8-0 nylon suture under microscope. When a partial liver graft

with multiple HAs is encountered, a standardized process to decide whether all HAs should be reconstructed is applied: first, sufficient arterial communication between the HAs is assessed during the donor procedure. After completing parenchymal dissection, the smaller HA is divided and checked for pulsatile back-bleeding from the graft side, while the larger HA is intact. Afterward the presence of pulsatile back-bleeding is then double-checked, this time in the recipient. Larger branches are reconstructed first, and smaller branches were assessed for the presence of pulsatile back-bleeding. If there is sufficient back-bleeding, arterial anastomosis is not performed for the smaller branch and intrahepatic arterial flow is finally assessed with intra-operative Doppler ultrasound (DUS). If sufficient intrahepatic arterial flow is detected, the smaller HA stump is ligated. When sufficient intrahepatic arterial flow is not detected, the smaller branch is reconstructed.

Bile duct anastomosis

In biliary atresia cases, biliary reconstruction was performed by hepaticojejunostomy (HJ). In recipients with normal bile duct, duct-to-duct anastomosis was considered first. HJ was performed when the recipient's bile duct was too small or when there was marked size discrepancy of bile duct between donor and recipient. There were 13 cases of duct-to-duct anastomosis. Five were Wilson's disease cases, five were fulminant hepatitis cases, one was angiosarcoma, one was hemangioendothelioma, and one was hepatocellular carcinoma,

Post-transplant management

The immunosuppression protocol and prophylaxis against viral infection after pediatric LDLT are described elsewhere [17]. Anticoagulation therapy with prostaglandin E1 (2 $\mu\text{g}/\text{kg}$) and low-molecular weighted heparin (50 $\mu\text{g}/\text{kg}$) is administered intravenously immediately following reperfusion of the liver graft, and these are continued for 7 days. Follow-up DUS after transplantation is routinely performed on post-transplant 1, 3, 5, 7, and 14 days and then every three months for three years. DISIDA scan is performed on the 14th postoperative day.

Hepatic artery stenosis is diagnosed when a tardus parvus pattern is shown on DUS and narrowed arterial segment is confirmed with computed tomography angiography. Bile leakage is defined as bile-colored fluid in closed suction drainage with a total bilirubin count

greater than 10-fold that of serum after the 7th postoperative day. BAS was defined as dilated intrahepatic bile duct and narrowed anastomosis site confirmed by percutaneous transhepatic cholangiography on the basis of abnormal liver function tests (e.g., blood alkaline phosphatase and bilirubin).

Statistical analysis

Survival rates were estimated by the Kaplan–Meier method and compared by log-rank test. Kruskal–Wallis analysis was used to compare three independent continuous variables, and the chi-square test was used for categorical variables. Potential univariate risk factors of BAS were analyzed using Cox regression analysis and log-rank test. Variables with a *P* value of <0.2 at the univariate level were included in a Cox multivariable proportional hazards model. The level of significance was set at 0.05. Statistical analysis was performed with SPSS version 22.0 (IBM, Armonk, NY, USA).

Results

Patient characteristics

The patient and operative characteristics of the three groups are shown in Table 1 and Table 2. The median size of donor HAs was smaller in Group 2 (multiple HAs with total reconstruction) compared with Group 1 (single HA, *P* < 0.001) and Group 3 (multiple HAs with partial reconstruction) (*P* = 0.001). The duration of the

HA reconstruction procedure was longer in Group 2 compared with Group 1 (*P* < 0.001) and Group 3 (*P* = 0.03). Other variables were not significantly different among all three groups.

Patient and graft survival

Outcomes after pediatric LDLT are summarized in Table 3. There were 13 cases (9.6%) of graft failure and 16 patient deaths (11.8%). Overall, the 1-year, 5-year, and 10-year graft survival rates were 93.4% (89.3–97.6), 91.8% (87.2–96.6), and 89.3% (83.9–95.2), respectively. Patient survival rates at 1-year, 5-year, and 10-year were 93.4% (89.3–97.6), 88.8% (83.6–94.3), and 87.7% (82.1–93.6), respectively. Graft survival and patient survival were not significantly different among the three groups (*P* = 0.226, *P* = 0.880, respectively, Figure 1). The causes of graft failure were hepatic vein thrombosis, HCV reactivation, portal vein thrombosis, BAS with recurrent cholangitis, steroid pulse therapy resistant acute rejection, postoperative bleeding, large for size graft, and hepatic artery occlusion. In two cases, the causes of liver failure were not identified.

Hepatic artery complications

There were 4 cases (2.9%) of HA stenosis, two of which were related to HAT. Three cases occurred in Group 1, and one case was in Group 3. HA stenosis-free survival rates were comparable among the three groups (*P* = 0.598, Figure 2). Operation was needed in two

Table 1. Patients characteristics.

	Group 1 (<i>n</i> = 74)	Group 2 (<i>n</i> = 23)	Group 3 (<i>n</i> = 39)	<i>P</i> -value
Recipient				
Age – month, median (range)	12 (4–168)	8 (4–36)	11 (4 to 132)	0.029
Sex – M:F	28:46	7:16	19:20	0.369
BMI – kg/m ² median (range)	16.6 (11.5 to 30.0)	16.4 (13.4 to 23.3)	16.4 (9.8 to 21.5)	0.503
Donor				
Age – years, median (range)	34 (21 to 62)	33 (28 to 42)	32 (20 to 42)	0.256
Sex – M:F	39:35	10:13	21:18	1.000
Cause of LT				
Biliary atresia – <i>n</i> (%)	53 (71.6)	21 (91.3)	24 (61.5)	0.240
LC – <i>n</i> (%)	4 (5.4)	0 (0)	1 (1.4)	
HCC – <i>n</i> (%)	1 (1.4)	0 (0)	0 (0)	
Autoimmune dz. – <i>n</i> (%)	1 (1.4)	0 (0)	3 (7.7)	
Fulminant hepatitis – <i>n</i> (%)	9 (12.2)	1 (4.3)	5 (12.8)	
Metabolic dz. – <i>n</i> (%)	2 (2.7)	0 (0)	5 (12.8)	
Other malignancy – <i>n</i> (%)	4 (5.4)	1 (4.3)	1 (2.6)	
CTP score – median (range)	8 (5 to 13)	8 (5 to 11)	8 (5 to 12)	0.926
PELD score – median (range)	16 (–7 to 53)	14 (–7 to 39)	13 (–10 to 64)	0.653

Table 2. Surgical factors.

	Group 1 (n = 74)	Group 2 (n = 23)	Group 3 (n = 39)	P-value
Macro-fatty change – %, median (range)	5 (0–25)	5 (1–30)	5 (0–30)	0.240
Micro-fatty change – %, median (range)	5 (0–65)	5 (1–40)	10 (0–30)	0.392
BD size – mm, median (range)	5.0 (2.0–10.0)	5.0 (2.0–8.0)	5.5 (1.0–10.0)	0.910
BD anastomosis number	Single – n (%)	20 (87.0)	38 (97.4)	0.267
	Double – n (%)	0 (0)	1 (2.6)	
BD anastomosis type	DD – n (%)	0 (0)	6 (15.4)	0.510
	HJ – n (%)	67 (90.5)	33 (84.6)	
		7 (9.5)	4 (10.3)	
Ductoplasty – n (%)	7 (9.5)	4 (17.4)	4 (10.3)	0.877
Hepatic artery size – mm, median (range)	2.0 (1.5–3.5)	1.5 (1.0–2.0)	2.0 (1.5–3.0)	0.000
GRWR – %, median (range)	2.7 (1.0–5.0)	3.0 (1.0–5.0)	3.1 (1.0–6.0)	0.121
CIT – min, median (range)	51 (16–155)	52 (17–103)	63 (13–170)	0.566
WIT – min, median (range)	29 (15–58)	32 (20–66)	30 (18–67)	0.654
OP time – min, median (range)	470 (340–871)	475 (420–560)	470 (370–720)	0.753
Hepatic artery anastomosis time – min, median (range)	23 (10–65)	56 (24–95)	28 (10–105)	0.000
Bile duct anastomosis time – min, median (range)	23 (10–40)	24 (11–110)	20 (10–108)	0.627

Table 3. Outcomes.

	Group 1 (n = 74)	Group 2 (n = 23)	Group 3 (n = 39)	P-value	
AST – IU/L, median (range)	573 (91–19 000)	583 (212–1304)	812 (188–12 925)	0.139	
ALT – IU/L, median (range)	511 (135–7800)	454 (186–1094)	607 (125–15 373)	0.118	
Graft failure (%)	8 (10.8)	0 (0)	5 (12.8)	1.000	
Patient loss (%)	9 (12.2)	2 (8.7)	5 (12.8)	1.000	
HA stenosis (%)	3 (4.1)	0 (0)	1 (2.6)	0.813	
Biliary complications (%)					
	Leakage	0 (0)	0 (0)	2 (5.1)	0.081
	Stricture	6 (8.1)	0 (0)	3 (7.7)	0.851

cases, and HA flow was restored in one case. In two cases, conservative management with an antiplatelet agent led to improved liver function.

Biliary complications

Biliary leakage was detected in 2 cases (1.5%), both in Group 3. Both cases were managed with percutaneous closed suction drainage and neither case proceeded to BAS. BAS was detected in nine cases (6.6%), all of which were managed with percutaneous transhepatic biliary drainage. Biliary stricture-free survival rates were comparable among the three groups ($P = 0.389$, Figure 2).

Biliary anastomosis stricture risk factor analysis

To assess risk factors for biliary stricture, a log-rank test was used for categorical variables and Cox regression analysis was used for continuous variables. Multivariate

analysis was performed for factors with P values of <0.2 . Bile duct diameter <5 mm was the only significant risk factor of biliary stricture in multivariate analysis (Table 4). However, the presence of multiple HAs or partial reconstruction of multiple HAs was not significant risk factors for BAS.

Discussion

The results of this study demonstrate that partial reconstruction of HAs in pediatric LDLT using a left liver grafts with multiple HA stumps did not affect overall patient survival, graft survival, biliary complication rate, or arterial complication rate when sufficient pulsatile back-bleeding from the smaller artery was demonstrated within the donor and recipient and DUS confirmed intrahepatic arterial flow after completion of arterial anastomosis. Multiple HAs alone and partial reconstruction of multiple HAs were not risk factors of BAS. We believe our protocol of verifying sufficient back-bleeding

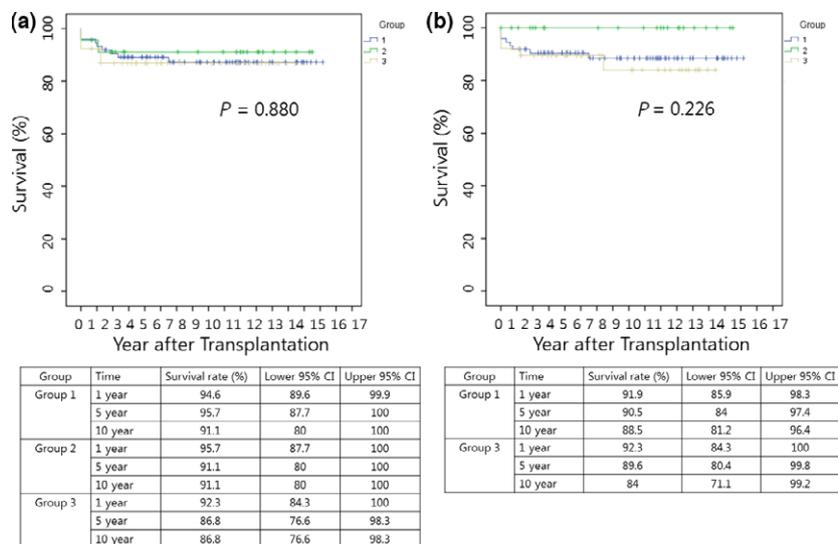


Figure 1 Patient and graft survival rate. (a) patient survival rate and (b) graft survival rate. Table shows survival rate and 95% confidence interval at 1, 5, and 10 year after transplantation.

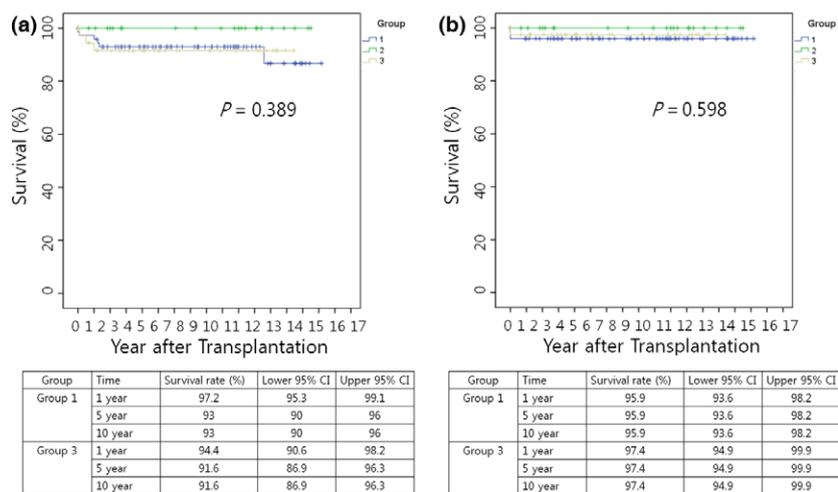


Figure 2 Biliary anastomosis stricture and hepatic artery stenosis-free survival rate. (a) biliary anastomosis stricture-free survival rate and (b) hepatic artery stenosis-free survival rate. Table shows survival rate and 95% confidence interval at 1, 5, and 10 year after transplantation.

from the smaller artery, while a graft is within the donor and then within the recipient was an important factor contributing to the successful outcome of our pediatric LDLT recipients receiving grafts with multiple HAs.

Liver grafts generally have fine intrahepatic arterial networks, and re-arterialization through interlobar collateral arteries can compensate for one ligated HA [18–20]. Therefore, even partial reconstruction of multiple HAs may be enough to maintain sufficient arterial flow to liver grafts and this idea has been attested by previous studies [3,11]. However, strenuous effort must be made to ensure that there is, in fact,

sufficient intrahepatic arterial network. We confirmed the presence of an intrahepatic arterial network by observing pulsatile back-bleeding from the smaller artery within the donor and the recipient, as well. In our cohort of pediatric LDLT recipients, outcomes were not different between Group 2 (multiple HAs with total reconstruction) and Group 3 (multiple HAs with partial reconstruction) in terms of graft and patient survival, HA stenosis, or biliary stricture. We believe our protocol of confirming the presence of an intrahepatic arterial network may be a practical guideline for decision making in reconstruction of multiple HAs.

Table 4. Risk factor analysis for biliary stricture.

Number of event = 9	Univariate analysis			Multivariate analysis		
	P-value	HR	CI	P-value	HR	CI
Donor age	0.213					
Recipient age	0.582					
Donor male sex	0.122			0.955	461.092	0.000–5.314E+201
Recipient male sex	0.068			0.074	5.174	0.852–31.405
GRWR	0.720					
PELD score	0.827					
CTP score	0.523					
Previous Kasai operation	0.923					
Ductoplasty	0.266					
Number of bile duct anastomosis	0.142			0.621	1.959	0.137–28.095
Duration of bile duct anastomosis	0.742					
Size of donor bile duct < 5 mm	0.052			0.020	10.211	1.446–72.105
Multiple hepatic artery	0.506					
Partial hepatic artery reconstruction	0.641					
Hepatic artery stenosis/thrombosis	0.763					
CMV infection	0.368					
CIT (min)	0.821					
WIT (min)	0.864					
Operation time (min)	0.009	1.009	1.002–1.016	0.087	1.010	0.999–1.021

With recent technical advancements in arterial anastomosis using microscopes and surgical loupes with high magnification ($\times 3.5$ – 4.5), it is possible to reconstruct all HAs in most cases [6,7]. However, liver grafts with multiple HAs usually have smaller caliber arteries and reconstruction of multiple HAs significantly lengthens HA anastomosis time, as was the case in our patients (Table 2). Smaller arteries and longer anastomosis time are known risk factors of HAT [16,21]. The results of our analysis suggest that partial reconstruction of multiple HAs is able to shorten the anastomosis time without the statistical difference in the rate of arterial and biliary complications as long as there is sufficient intrahepatic communication between hepatic arteries.

Post-transplant biliary complications occur in 9–40% of LDLT recipients, but the reported incidence differs considerably between centers [22]. In pediatric patients, biliary complication rates tend to be lower than in adult patients. Chen *et al.* [23] reported a 7% biliary complication rate during a mean follow-up period of 85.5 months while D'Alessandro *et al.* [24] reported a 15.8% biliary complication rate during 20 years. This difference could be influenced by biliary reconstruction methods [25]. Most studies debating the safety of partial reconstruction of multiple HAs were performed with adult recipients [3,11,14]. Biliary reconstruction of pediatric LDLT was mainly performed as hepaticojejunostomy (HJ). In this study, HJ was performed in 123 cases (90.4%). However, duct-to-duct anastomosis (DD) is performed in most

adult LDLT cases. Therefore, the results of previous studies based on adult cases are difficult to be extrapolated to pediatric patients. Suehiro *et al.* [13] performed all biliary reconstruction as HJs and reported a higher BAS rate in the partial reconstruction of multiple HAs group for adult LDLT. The complication rate was 43.2%, which is very different from the result of our study. Julka *et al.* [12] reported the safety of single HA reconstruction in pediatric LDLT. In that study, biliary reconstruction was performed by HJ (77 cases, 88.5%), and single HA reconstruction did not increase the risk of BAS. The overall incidences of biliary stricture and leakage were 9.19% and 8%, which were comparable to our results.

Although our data spanned nearly 15 years and provided a relatively large number of patients, there are drawbacks to using data from such a long period. Improvements in care and technology in postoperative management have occurred. Waiting time, donor availability, immunosuppression, and surgical techniques have all changed during this time. Due to the retrospective design of this study, there were incomplete or missing data, especially in earlier cases. This study deducted its conclusion with respect to survival-type outcomes. However, the statistical power of such analysis is not high enough to draw firm conclusions. Additional studies including more patients and events will be necessary. Despite its limitations, to the best of our knowledge, this study enrolled the largest number of pediatric LDLT cases using liver grafts with multiple HA.

Conclusion

In pediatric LDLT, partial reconstruction of HAs in left liver grafts with multiple HA stumps does not increase BAS risk or affect graft survival when intrahepatic arterial communication is confirmed by a standardized protocol of observing pulsatile back-bleeding from the smaller artery and DUS.

Authorship

Kyo Won Lee: study design, data collection, data analysis, and writing of this article. Sanghoon Lee: study design, data collection, data analysis, and reviewing the

article. Dong Kyu Oh, Byung Gon Na, Jin Yong Choi, Wontae Cho, and Seunghwan Lee: data acquisition. Jong Man Kim, Gyuseong Choi, and Choon Hyuck David Kwon: reviewing the article. Jae-Won Joh and Suk-Koo Lee: study design and reviewing the article.

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Conflicts of interest

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