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The rate of hepatic artery complications is higher in pediatric liver transplant recipients with metabolic liver diseases than with biliary atresia☆,☆☆,★

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ABSTRACT

Background: Liver transplantation (LT) is an excellent treatment option for patients with biliary atresia (BA) who fail portoenterostomy surgery. LT is also increasingly performed in patients with metabolic liver diseases. This study compared the outcomes in pediatric patients who underwent LT for metabolic liver diseases and BA.
Basic procedures: Data from 237 pediatric patients who underwent primary LT at Seoul National University Hospital from 1988 to 2015, including 33 with metabolic liver diseases and 135 with BA, were retrospectively analyzed.
Main findings: Compared with children with BA, children with metabolic liver diseases were significantly older at the time of LT (121.3 vs. 37.3 months; $P < 0.001$), and had lower Child–Pugh (7.1 vs. 8.4; $P = 0.010$) and Pediatric End-stage Liver Disease (6.5 vs. 12.8; $P = 0.042$) scores. Overall survival rates were similar (87.8% vs. 90.8%; $P = 0.402$), but hepatic artery (HA) complications were significantly more frequent in children with metabolic liver diseases (12.1% vs. 1.5%; $P = 0.014$).
Principal conclusion: Despite similar overall survival, children with metabolic liver diseases had a higher rate of HA complications.
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Biliary atresia (BA) is a childhood disease characterized by a progressive and fibroinflammatory process that affects the bile ducts. The primary initial surgical treatment is the Kasai procedure, which reestablishes bile flow and prevents rapid progression to biliary cirrhosis. If this procedure is not curative [1,2], liver transplantation (LT) can restore synthetic function, with BA being the most common indication for pediatric LT [3–5].

Metabolic diseases resulting from inborn errors of metabolism are characterized by the production of toxic intermediates. LT in children with metabolic diseases corrects the underlying metabolic defect, preventing life-threatening liver failure and/or improving quality of life. At the time of LT, children with metabolic diseases are generally in better clinical condition than children with other chronic liver diseases [6,7]. The accumulation of experience, the development of surgical techniques and immunosuppressants, and improvements in posttransplant outcomes have enabled successful LT in children with a broader range of metabolic diseases. Metabolic diseases have become the second most frequent indication for pediatric LT, following BA [6,8].

Abbreviations: BA, biliary atresia; DDLT, deceased donor liver transplantation; HA, hepatic artery; GRWR, graft-versus-recipient weight ratio; HAS, hepatic artery stenosis; HAT, hepatic artery thrombosis; CTA, computed tomography angiography; LDLT, living donor liver transplantation; LHA, left hepatic artery; MHA, middle hepatic artery; RHA, right hepatic artery; LT, liver transplantation; PELD, Pediatric End-stage Liver Disease; POD, postoperative day; SD, standard deviation; KONOS, Korean Network for Organ Sharing.

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This study was designed to compare complications and survival rates in pediatric patients who underwent LT for BA and metabolic diseases at a single center.

1. Patients and methods

The institutional review board of Seoul National University Hospital approved this retrospective cohort study (IRB no. H-1707-055-867) and waived the requirement for informed consent. From March 1988 to September 2015, 248 patients aged <18 years underwent LT at Seoul National University Hospital, including 237 who underwent primary LT. Children who underwent LT for indications other than BA and metabolic diseases were excluded. The medical records of all included patients were retrospectively reviewed.

To reduce any bias related to experience with LT, the study period was subdivided into three time periods: an early period, during which the LT program at our center was launched (1988–2007); the middle period, during which survival outcomes of LT improved and living donor data were prospectively collected (2008–2011); and the recent period, during which recipient data were prospectively collected, the pediatric LT protocol was designed, a specialized team for pediatric LT was created, and the number of recipients undergoing split LTs had increased (2012–2015).

1.1. Surgical technique

To avoid large-for-size graft syndrome, graft volume in living donors was measured by CT volumetry before living donor LT (LDLT); in split liver donors to small children weighing less than 10 kg, graft volume was measured by enhanced CT scans. If the graft-versus-recipient weight ratio (GRWR) was greater than 4% in children with portal hypertension or greater than 3% in patients without portal hypertension and a flat belly, the donor surgeon used enhanced CT scans to reduce the graft size using an in situ technique based on preoperative plans for a monosegment or reduced graft. In patients undergoing emergency deceased donor LT (DDLT) in the absence of enhanced CT scans of the donor, the recipient surgeon reduced the graft in situ after reperfusion, fitting the graft to the recipient peritoneal cavity. A cavitron ultrasonic device was used for graft reduction.

The surgical technique used for pediatric LT involved a piggyback method. The hepatic vein and portal vein were each anastomosed using a continuous suture technique with PDS (6-0 or 5-0). The proper hepatic artery (HA) was used for whole LT, and the right HA (RHA) was used for right-sided liver grafts in both LDLT and split LT. The left and middle HAs (LHA and MHA) were reconstructed for left-sided liver grafts in both LDLT and split LT. The MHA was usually included in left lateral section grafts because, although uncommon, an aberrant segmental artery for segment 2 or 3 may have arisen from the MHA. Moreover, the MHA is important for monosegment LT in small children, especially in those undergoing split LT in the absence of preoperative donor images. In cases with a pulsatile back flow, the replacement HA was not reconstructed. In all other cases, the HA was reconstructed under a surgical microscope by one of three plastic surgeons with more than 5 years of experience, with microscopic surgery performed using an interrupted suture technique with 9-0 or 10-0 nylon strings.

1.2. Post-LT management

Following surgery, patients were administered tacrolimus and steroid as dual immunosuppressants, with steroid tapered off over 6 months. Patients were evaluated once daily for 7 days and twice weekly during hospital stay by posttransplant liver Doppler.

Anticoagulation in children did not include systemic heparinization or subcutaneous injection of low molecular weight heparin. Aspirin was administered to prevent vascular thrombosis to patients with a platelet count higher than $50 \times 10^3/mm^3$ and a prothrombin time–international normalization ratio less than 2. Aspirin was maintained for 1 year or to age over 5 years.

Major complications of greater than grade 3 were recorded. Complications of hepatic vein and portal vein (thrombosis and stenosis) and accompanying clinical problems (e.g., abnormal laboratory data or clinical symptoms) were defined as imaging abnormalities requiring intervention. Venous complications were first treated by nonsurgical radiologic intervention (balloon angioplasty or stent insertion) without additional anticoagulation, except in patients with acute complete portal vein thrombosis. These latter patients initially underwent surgical thrombectomy with 1 day systemic heparinization.

HA complications included HA thrombosis (HAT) and HA stenosis (HAS); the former was diagnosed as an occluding thrombus without intrahepatic flow and the latter was diagnosed as a resistance index <0.5 and a systolic acceleration time > 0.08 s with tardus parvus waveform on postoperative liver Doppler [9,10]. Patients with HA complications were treated using a management algorithm (Fig. 1). If liver Doppler showed HA thrombosis, conventional or computed tomographic angiography (CTA) was immediately performed. If liver Doppler showed abnormal findings other than HAT, liver Doppler and liver function tests were repeated within 12 h. If an HA complication was still suspected, CTA or conventional angiography was performed. If angiography detected intrahepatic arterial flow, liver Doppler and liver function tests were repeated within 24 h. Patients with complications were treated conservatively, including with aspirin, dipyridamole, or prostaglandin E1. If HA flow could not be visualized or liver function tests showed exacerbation of associated clinical problems (e.g., biliary complications or deterioration of graft function), surgical intervention was performed.

Biliary complications (ascending cholangitis, stenosis, and leakage) and accompanying clinical problems (e.g., abnormal laboratory data or clinical symptoms of pain, fever, or an itching sensation) were defined as imaging abnormalities requiring intervention. Biliary complications were first treated by a nonsurgical radiologic intervention (endoscopic or percutaneous drainage), along with administration of antibiotics.

1.3. Statistical analysis

Results were expressed as means and standard deviations (SD) or as numbers and percentages. Continuous variables were compared using Student's t-tests, and categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Patient and graft survival rates were calculated using the Kaplan–Meier method and compared using the log-rank test. Potential univariate predictors of survival were analyzed by Cox regression analysis. *P*-values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS software (version 22; SPSS Inc., Chicago, IL, USA).

2. Results

2.1. Baseline characteristics

Of the 237 children who underwent primary LT at our center between March 1988 and September 2015, 135 underwent LT for BA and 33 for metabolic diseases. The proportion undergoing LT for metabolic diseases has increased over time, from 9.4% during the early period to 16.2% during the middle period and 20.7% during the recent period (Fig. 2). Of the 33 children who underwent LT for metabolic diseases, 11 each (33.3%) had Wilson disease and type 1 glycogen storage disease, and seven (21.2%) had primary hyperoxaluria type I, with the remaining patients having other diseases, including factor H deficiency (n = 2), tyrosinemia (n = 1), and hemochromatosis (n = 1) (Fig. 3A). Overall survival rates did not differ significantly in the groups of patients with metabolic diseases ($P = 0.861$) (Fig. 3B).

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