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Staged biliary reconstruction after liver transplantation: A novel surgical strategy for high acuity pediatric transplant recipients[☆]

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ABSTRACT

Introduction: Biliary complications after pediatric orthotopic liver transplantation remain causes of significant patient morbidity. Staged operative approach in complex hepatobiliary surgery has improved postoperative outcomes but has not been evaluated in pediatric orthotopic liver transplantation. We sought to analyze the outcomes of staged biliary reconstruction after orthotopic liver transplantation in high acuity patients.
Methods: A retrospective analysis of 43 pediatric orthotopic liver transplantations at our center (January 2013 through December 2017). Median follow-up was 25 months. Variables were compared for group I: 1-stage orthotopic liver transplantation with biliary anastomosis ($n = 6$) versus group II: staged biliary reconstruction orthotopic liver transplantation ($n = 37$).
Results: Comparing groups I and II, median age (7.3 vs 4.8 years), weight (27 vs 19 kg), proportion of urgent orthotopic liver transplantation (50% vs 65%), partial graft orthotopic liver transplantation (33% vs 35%), and intraoperative red blood cell transfusion volume (11 vs 21 mL/kg) were comparable. Roux-en-Y hepaticojejunostomy was performed in 67% (group I) and 49% (group II). There was no biliary complication in both groups. For groups I and II, 3-year survival rates for graft (100% vs 92%, $P = .477$) and patient (100% vs 97%, $P = .679$) were comparable.
Conclusion: Our study showed excellent outcomes with staged biliary reconstruction orthotopic liver transplantation in high acuity pediatric transplant recipients. This is the first report showing clinical applicability of staged biliary reconstruction orthotopic liver transplantation in children.

Introduction

In the early days of orthotopic liver transplantation (OLT), biliary reconstruction was described as the “Achilles’ heel” of the procedure.[1] Biliary complications after OLT, with an incidence of 10–45%, is strongly associated with inferior patient outcomes and increased health care cost.[2,3] For pediatric patients, the risk of biliary complications after OLT, such as leaks and strictures, is particularly significant because of the small and fragile bile ducts.[4–9] Although surgical refinements have resulted in improvement of outcomes, nontechnical risk factors also contribute substantially to the development of biliary complications after OLT. These factors include compromised hepatic arterial flow, severe malnutrition, coagulopathy, use of high doses of steroids for immunosuppression, prolonged cold organ preservation duration, and immunological factors.[5,7,8] Furthermore, critically ill patients frequently exhibit hemodynamic instability, severe metabolic derangement, hypothermia, visceral edema, and bowel distention during OLT, rendering them at increased risk for biliary complications when biliary reconstruction is performed under these conditions.[10–14]

Staged operative approach in complex hepatobiliary surgery has improved postoperative outcomes. For example, a 2-stage hepatectomy strategy minimizes the risk of postoperative liver failure

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resulting from insufficient remnant liver and allows a safer aggressive curative hepatic resection of an initially unresectable hepatic tumor.[15–18] In high acuity patients undergoing OLT, a 2-stage OLT with delayed biliary reconstruction offers the benefit of performing the biliary reconstruction a few days after OLT under a more stable hemodynamic state and favorable operative milieu, minimizing the risk of biliary complications. Although the utility of a 2-stage OLT with delayed biliary reconstruction has been reported in adult OLT, this operative approach has not been evaluated in pediatric recipients.[19,20] We sought to analyze the utility and outcomes of staged biliary reconstruction orthotopic liver transplantation (SBRALT) in high acuity pediatric transplant recipients.

Methods

Data collection

We performed a retrospective review from our prospective transplantation database of all pediatric patients (<18 years of age) who underwent OLT at the Medical College of Wisconsin–Children's Hospital of Wisconsin from January 1, 2013 to December 31, 2017. The median follow-up was 25 months. The Medical College of Wisconsin Institutional Review Board approved the study.

Patient, donor, and operative variables

Variables collected for analysis included for both patients and donors included age, ethnicity, gender, history of diabetes mellitus, body mass index. For recipients, variables collected for analysis included indication for OLT, number of previous OLT, Model for End-Stage Liver Disease / Pediatric End-Stage Liver Disease score or United Network for Organ Sharing status 1 category at time of OLT, whether the patient received a whole or partial hepatic graft, vasopressors and ventilator support, and serum albumin (as a surrogate for the nutritional status and severity of liver graft dysfunction) at time of OLT, and previous major abdominal surgery. For this study, major abdominal surgeries only included previous OLT, hepatic resection, hepatoportoenterostomy (Kasai procedure), bowel resection, Nissen fundoplication, and bilateral native nephrectomy. For donors other procedures, such as cholecystectomy, open liver biopsy, gastric tube placement, and appendectomy, were not considered major abdominal procedures; length of hospitalization before donation, cause of death, need for vasopressors befire donation, and donor type (deceased versus live donor). Operative variables included in the analysis were type and timing of biliary reconstruction (one stage versus SBRALT), graft cold and warm ischemia times, body temperature of the patient, acid–base status, presence of intra-abdominal adhesions, visceral edema or bowel distention, the need for veno-venous bypass, blood transfusion requirement, and post-perfusion syndrome.

Timing and technique of biliary reconstruction

The surgical procedure for OLT was performed in a standard manner as previously described.[6] A one-stage OLT with biliary anastomosis at the same time of transplantation was initially intended for all patients. SBRALT was instituted for patients who exhibited the following during OLT before biliary reconstruction: hemodynamic instability requiring high doses of vasopressive agents, severe coagulopathy requiring massive transfusion of blood products, metabolic acidosis, hypothermia, the additional need for an extensive lysis of intra-abdominal adhesions, and significant visceral edema and bowel distention. Before abdominal wall closure, a hepatic allograft cholecystectomy was performed and a biliary catheter was inserted into the hepatic allograft bile duct and secured with 6-0 Prolene suture. The biliary catheter was externalized and secured to the skin.

The second stage of biliary reconstruction, either choledocho-choledochostomy (duct-to-duct) or Roux-en-Y hepaticojejunostomy, was performed between 1 and 6 days after OLT once the patient achieved hemodynamic stability, improvement of hepatic allograft function, and reduction or resolution of visceral edema or bowel distention. The choledocho-choledochostomy was accomplished with interrupted stiches using monofilament absorbable sutures. In cases of size mismatch between the native and donor bile ducts, ductoplasty was performed. For the biliary anastomosis, the posterior bile duct wall stitches were placed before those for the anterior wall and all the sutured knots were tied extraluminally. T-tube or internal biliary anastomotic stent were utilized selectively. Whereas T-tubes were used for patients with larger native bile ducts, long internal biliary stents that extended into the duodenum were placed for diminutive native bile ducts. For patients with T-tube, a T-tube cholangiography was performed 5 days after biliary reconstruction and capped if cholangiogram demonstrated normal findings and the serum total bilirubin level had decreased to <5 mg/dL. At 3 months after OLT, a follow-up T-tube cholangiography was performed at the radiology suite. If the cholangiogram showed normal findings, the T-tube was removed, and an intra-abdominal drain was placed via the same T-tube track. The tip of the intra-abdominal drain was placed adjacent (extraluminal) to the exit site of the T-tube from the native bile duct. The intra-abdominal drain was connected to an extracorporeal bag. The purpose of this intra-abdominal drain was to remove any bile leak from the previous exit site of the T-tube immediately after T-tube removal. This drain is withdrawn at the bedside for an approximately 1–2 cm every 2 hours until it is completely removed. For patients with long internal biliary stent, endoscopic retrieval of the internal stent was performed at 3 months post-OLT.

For the Roux-en-Y hepaticojejunostomy, the biliary anastomosis was also accomplished with interrupted stitches using monofilament absorbable sutures. A short internal biliary anastomotic stent was placed and secured with a monofilament absorbable suture. After degradation and absorption of the absorbable anchor suture, the short internal biliary stent spontaneously dislodged and passed through the gastrointestinal tract.

Outcome measures

The outcomes of OLT patients who underwent 1-stage OLT with biliary reconstruction at the same time of OLT (group I) were compared to those who received SBRALT (group II). The primary endpoint was 3-year graft-failure–free patient survival. Graft failure was defined as either the need for retransplantation or death owing to primary graft nonfunction or biliary complication. Secondary outcome measures focused on biliary complications, either biliary anastomotic leak or stricture. The surveillance for biliary complication was primarily based on clinical assessment that included blood chemistry test and abdominal drainage monitoring.

Statistical analysis

Graft-failure–free survival curves were computed using Kaplan-Meier methods using log-rank tests. Continuous variables were compared using the Mann-Whitney test and summarized as medians and interquartile ranges. Categorical variables were compared using a chi-squared or Fisher's exact test and summarized as percentages. Statistical analysis was performed using SPSS version 22 (SPSS, Inc., Chicago, IL).

Table 1
Recipient characteristics and pre-transplant medical status.

Characteristics	Group I ($n = 6$)	Group II ($n = 37$)	P value
Age, median, y (IQR)	7.3 (3.0–9.7)	4.8 (2.0–9.5)	.649
Male sex, no. (%)	1 (17)	20 (54)	.185
Weight, median (IQR), kg	27 (15–28)	19 (12–28)	.700
Height, median (IQR), cm	125 (90–131)	105 (82–133)	.713
Prior major abdominal surgery, no. (%)	2 (33)	16 (43)	1.000
Kasai procedure, no. (%)	1 (17)	9 (24)	
Hepatic resection, no. (%)	0	1 (3)	
Nissen fundoplication, no. (%)	0	1 (3)	
Bilateral native nephrectomy, no. (%)	1 (17)	2 (5)	
Small bowel resection, no. (%)	0	1 (3)	
OLT (retransplantation), no. (%)	0	2 (5)	
Diagnoses			.487
Biliary atresia, no. (%)	1 (17)	9 (24)	
Acute liver failure, no. (%)	1 (17)	7 (19)	
Hepatoblastoma, no. (%)	1 (17)	6 (16)	
α-1 antitrypsin deficiency, no. (%)	2 (33)	4 (11)	
Others, no. (%)	1(17)	11 (30)	
Status 1A and 1B, no. (%)	3 (50)	24 (65)	.655
MELD/PELD at OLT, median (IQR)	9 (8–21)	25 (13–28)	.636
Bilirubin, median (IQR), mg/dL	4.6 (1.6–7.1)	1.9 (0.6–15.4)	.902
INR, median (IQR),	1.5 (1.3–1.7)	1.3 (1.1–2.2)	.587
Albumin, median (IQR), g/L	3.9 (3.5–3.9)	3.4 (2.7–4.0)	.364
Pre-OLT intensive care unit, no. (%)	4 (67)	20 (54)	.678
Pre-OLT mechanical ventilation, no. (%)	2 (33)	6 (16)	.308
Pre-OLT hemodialysis, no. (%)	0	4 (11)	1.000
Pre-OLT $\geq$2 vasopressors, no. (%)	0	1 (3)	1.000

MELD = model for end-stage liver disease; PELD = pediatric end-stage liver disease; INR = international normalized ratio of the prothrombin time

Table 2
Hepatic graft factors.

Factors	Group I ($n = 6$)	Group II ($n = 37$)	P value
Partial hepatic grafts, no. (%)	2 (33)	13 (35)	1.000
Live donor, no. (%)	1 (17)	4 (11)	
Deceased donor in situ split, no. (%)	1 (17)	9 (24)	
Graft weight, median (IQR), g	674 (474–771)	429 (368–603)	.202
Graft-to-recipient weight ratio, median (IQR), %	2.7 (2.5–3.5)	2.2 (1.7–3.0)	.114
Cold ischemia time, median (IQR), min	338 (334–343)	324 (270–364)	.618
Warm ischemia time, median (IQR), min	37 (36–39)	43 (39–48)	.028

Results

Transplant recipient characteristics and pre-transplant medical status

Among the 43 pediatric OLTs performed between January 1, 2013 and December 31, 2017, 6 (14%) patients underwent 1-stage OLT with biliary reconstruction performed at the same time of transplant, whereas 37 (86%) received SBRALT. The recipient characteristics and pretransplant medical status were similar for both groups (Table 1). The most common liver disease was biliary atresia (23%) followed by unresectable hepatoblastoma (16%) and alpha-1 antitrypsin deficiency (14%).

Hepatic graft factors

Deceased donor whole liver graft was utilized in 28 of 43 OLTs. Of the 15 (35%) partial hepatic grafts used, 10 (67%) were in situ split grafts from deceased donors and 5 (33%) from live donors (Table 2). The median graft-to-recipient weight ratio as well as the duration of graft cold ischemia were comparable between the 2 groups. The median graft warm ischemia duration was 37 minutes (IQR 36–39) in group I and 43 minutes (IQR 39–48) in group II, $P = .028$.

Operative factors

A total of 22 of 43 (51%) OLTs required Roux-en-Y hepaticojejunostomy. For those who underwent SBRALT, the interval between the OLT and biliary reconstruction was a median of 2 days (Table 3). The intraoperative body temperature after hepatic graft revascularization (before biliary reconstruction) was significantly lower for patients in group II compared to group I, $P = .012$.

Biliary reconstructions and vascular complications

Table 4 shows the type of biliary reconstructions for both groups. Short internal biliary stents were placed for all patients who underwent Roux-en-Y hepaticojejunostomy. For patients who required choledocho-choledochostomy, none in group I needed either T-tube or internal biliary stenting whereas 9 of 18 (50%) in group II required placement of T-tube or internal biliary stent. There was no biliary complication (biliary leak or stricture) after OLT in both groups.

The overall incidence of hepatic artery thrombosis (HAT) was 6.9% (3 of 43 OLT). All 3 cases of HAT occurred in patients in group II and were nonanastomotic intraparenchymal HAT. Among the HAT cases, only 1 patient developed allograft failure because of HAT, whereas the other 2 were successfully treated with hepatic arterial thrombectomy, thrombolysis, and redo of hepatic

Table 3
Operative factors.

Factors	Group I ($n=6$)	Group II ($n=37$)	P value
Roux-en-Y hepaticojejunostomy, no. (%)	4 (67)	18 (49)	.664
Interval between OLT and biliary reconstruction, median (IQR), days	0	2 (2–3)	<.001
RBC transfusion, median (IQR), mL	225 (38–368)	600 (150–1200)	.109
RBC transfusion per body weight, median (IQR), mL/kg	11 (3–13)	21 (11–46)	.091
Temperature at the beginning, median (IQR),°C	36.7 (36.4–36.9)	36.5 (36.1–37.0)	.092
Temperature at the end, median (IQR),°C	37.1 (36.9–37.4)	36.3 (35.8–36.8)	.012
The worst base deficit, median (IQR), mEq/L	−5.7 (−6.6 – −4.4)	−6.9 (−7.9 – −4.3)	.449
Base deficit at the end, median (IQR), mEq/L	−2.2 (−5.4 – −0.5)	−4.1 (−5.2 – −1.3)	.697

Table 4
Biliary reconstruction.

Type	Internal stent or T tube	Group I ($n=6$)	Group II ($n=37$)	P value
Roux-en-Y hepaticojejunostomy	Internal stent, no. (%)	4 (67)	18 (49)	.664
Choledocho-choledochostomy	None, no. (%)	2 (33)	9 (24)	.637
	T tube, no. (%)	0	3 (8)	1.000
	Internal stent, no. (%)	0	6 (16)	.571
Not performed*, no. (%)		0	1 (3)	1.000

* Biliary reconstruction was not performed because the patient developed allograft failure and underwent retransplantation of the liver.

arterial anastomosis. The patient who developed HAT and lost her first hepatic allograft was a 17-year-old female who underwent OLT with a deceased donor whole allograft for unresectable hilar tumor and infiltrative biliary cirrhosis. The biliary reconstruction was not performed because of intraoperative hemodynamic instability (Table 4). Shortly after OLT, she developed hypercoagulable state and subsequent pulmonary embolism and nonanastomotic extensive intraparenchymal HAT**.** Surgical thrombectomy and catheter-directed thrombolysis were unsuccessful and the patient developed hepatic allograft failure. The patient underwent a successful retransplantation of the liver, maintained on systemic anticoagulation, and continued to have normal function of her second hepatic allograft and patency of all vascular anastomoses.

The other 2 HAT cases were successfully treated with hepatic arterial thrombectomy, thrombolysis, and revision of hepatic arterial anastomosis. The first patient was a 9-month-old male, 6 kg in weight, who underwent OLT using a deceased donor (12-month-old, 8 kg) whole liver allograft for unresectable hepatoblastoma. SBRALT (Roux-en-Y hepaticojejunostomy) was performed on post-transplant day 2 and the patient developed hepatic graft intraparenchymal hepatic artery thrombosis on post-transplant day 5. The patient required takedown of an intact hepaticojejunostomy (without any complication) to gain adequate operative access and exposure to the hepatic artery (which was posterior to the hepaticojejunostomy). We performed a thrombectomy and thrombolysis of the intraparenchymal hepatic artery and successfully re-established optimal hepatic arterial flow. The Roux-en-Y hepaticojejunostomy was re-established without any complication. The second patient was a 4-year-old female who underwent a live-donor partial hepatic allograft (hepatic segment II and III) transplantation for congenital choledochal cyst (type IV). The biliary reconstruction was deferred because of intraoperative hemodynamic instability, persistent coagulopathy, and massive visceral edema. During the planned SBRALT on post-OLT day 2, a routine surveillance intraoperative Doppler ultrasound of the hepatic allograft demonstrated patient hepatic arterial anastomosis; however, suboptimal waveform of the intraparenchymal left hepatic artery was observed. A thrombectomy and thrombolysis of the non-anastomotic intraparenchymal left hepatic artery successful treated the arterial thrombus. A completion intraoperative Doppler ultrasound confirmed normal intraparenchymal hepatic arterial waveform. SBRALT (Roux-en-Y hepaticojejunostomy) was performed during the same operation. Both patients did well,

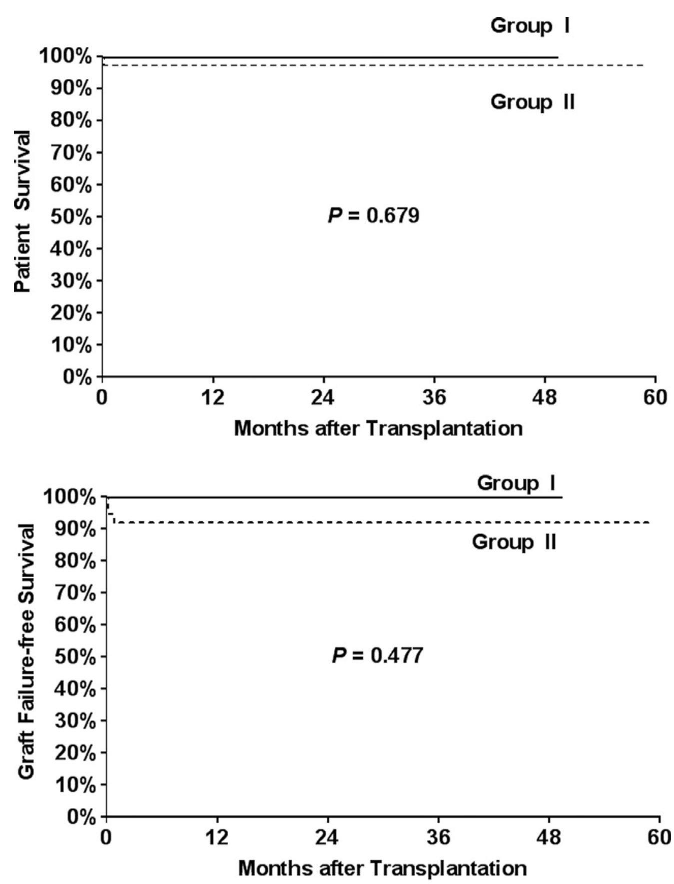

Fig. Patient and graft-failure–free survival after liver transplantation: group I (1-stage OLT) versus group II (SBRALT)

maintaining patency of the hepatic artery and exhibiting normal hepatic graft function without any long-term biliary complication.

Post-transplant outcomes

Comparing groups I and II, the duration of the hospitalization (median 15 days [IQR 13–30] vs 25 days [IQR 16–41], $P=.173$) and the need for intensive care management (median of 8 days [IQR 7–

13] and 12 days [IQR 8–21], $P = .083$) were similar. For Groups I and II, the 3-year survival rates for graft (100% vs 92%, $P = .477$) and patient (100% vs 97%, $P = .679$) were comparable (Fig). For group II, there was 1 patient who developed primary graft nonfunction and subsequently died while on the waitlist for a retransplantation of the liver.

Discussion

The pediatric liver transplant procedure is a highly complex operation owing to the need to preserve the integrity of the small donor organ and delicate structures (vascular and biliary) during organ procurement and to prepare its corresponding structures of the transplant recipient for vascular and biliary anastomoses in OLT. The complexity of the procedure is further increased with the use of partial hepatic grafts in children. As such, it is not surprising that the vascular and biliary complication rates in pediatric OLT are much higher compared to such rates in adults.[2–8]

Biliary complications after OLT in children are strongly associated with increased morbidity and inferior graft-failure–free outcome. Although the overall incidence of biliary complications after pediatric OLT ranges between 10–45%, several pediatric liver transplantation programs experienced much lower rates of 4–17%, even with the use of partial hepatic grafts from deceased and live donors.[5,6,21] Risk factors for biliary complications in children include the use of partial hepatic grafts, Roux-en-Y hepaticojejunostomy (as opposed to choledocho-choledochostomy), presence of multiple bile ducts in the liver graft, prolonged graft cold ischemia, and hepatic artery thrombosis.[5,22–24] Moreover, the transplant center's pediatric OLT volume and surgical expertise are critical factors that are associated with biliary and vascular complications after OLT.

The present study showed that the risk of biliary complications in pediatric OLT could further be reduced by utilizing a staged operative approach for complex pediatric OLT. The traditional 1-stage OLT with biliary reconstruction at the time of transplantation was initially intended for all patients undergoing OLT. The patient's suitability to proceed with 1-stage OLT was evaluated after hepatic graft reperfusion. SBRALT was performed for patients who met the following criteria: hemodynamic instability requiring high doses of vasopressive agents, severe coagulopathy requiring massive transfusion of blood products, metabolic acidosis, hypothermia, the additional need for an extensive lysis of intra-abdominal adhesions, and significant visceral edema and bowel distention. The second stage was performed approximately 2 days after graft implantation when the patient's hemodynamic and metabolic status had stabilized, body temperature had normalized, portal hypertension had almost (if not completely) resolved, coagulation had improved, the need for transfusion of blood products had reduced, and visceral edema and bowel distention had resolved.

In our study, there was no short- or long-term biliary complication during the follow-up period. Noteworthy is the absence of biliary complication despite the high utilization partial grafts (35%) and frequent need for Roux-en-Y hepaticojejunostomy (51%) in our patients. This surgical approach of 2-stage OLT with delayed biliary reconstruction provides an optimal operative milieu for biliary reconstruction. In addition to the benefit of performing the biliary reconstruction in a stable patient, we believe that the second stage procedure allows for secondary survey of the hepatic graft and vascular anastomoses. It is also noteworthy to mention that the shift of our liver transplantation program's practice from 1-stage to 2-stage (SBRALT) OLT reflects our recent programmatic growth in expanding medical access to high acuity small children in need of life-saving OLT. As such, patients who underwent SBRALT (compared to 1-stage OLT) tended to be younger and smaller with higher acuity of illness, received smaller hepatic allograft (whole and partial allografts), and experienced higher degrees of intraoperative hemodynamic instability and blood loss. Although these findings are encouraging, we acknowledge the limitations of this study. Specifically, the small sample size renders the possibility of a type II error in the statistical analysis. As such, additional studies with a larger cohort are necessary to draw comparisons between the 2 groups.

In conclusion, biliary leaks and strictures are serious complications after OLT that decrease patient and graft survival. Avoidance of these complications is critical to the success of OLT. To our knowledge, this is the first report showing clinical applicability and safety of SBRALT in children. Our study showed excellent outcomes of SBRALT in high acuity pediatric transplant recipients and is an important operative strategy in complex OLT in children.

Conflicts of interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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