Outcome of Pediatric Live-Donor Liver Transplantation—The Toronto Experience

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Background/Purpose: Live-donor liver transplantation (LDLT) has developed to address the critical shortage of cadaveric organs that accounts for 20% of children who die while awaiting for a liver transplant in Ontario each year. This report reviews the outcome of the pediatric recipients of LDLT at the authors' center.

Methods: The charts of all children who received a LDLT between June 1996 and March 2002 were reviewed retrospectively.

Results: Thirteen children (mean age, 3.6 years) underwent LDLT. All donors were parents except for one cousin. Ten grafts were left-lateral segments, 2 were right lobes, and 1 was a left lobe. Three patients required a SILASTIC® (Dow Corning, Midland, MI) patch for delayed abdominal wall closure. Patient and graft survival rate was 100% with a median follow-up of 376 days. Major postoperative complications included biliary leaks (n = 2), biliary strictures (n = 1), portal vein thrombosis (n = 1), and hepatic venous complications (n = 1). There were no cases of hepatic artery thrombosis. Ten of 12 children became Positive for Epstein-Barr virus (EBV), and 3 of these patients had readily treatable post-transplant lymphoproliferative disorder.

Conclusions: LDLT is an acceptable alternative to cadaveric transplantation for children with end-stage liver disease.
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INDEX WORDS: Liver transplantation, live donors, outcome.

LIVER TRANSPLANTATION has become the therapy of choice for patients with end-stage liver disease.[1,2] Recipient survival has improved dramatically over the past 20 years, largely as a result of technical innovations and advances in postoperative immunosuppression.[3] The major obstacle preventing the more widespread application of this lifesaving therapy is a critical shortage of donor organs. Historically, this shortage was most profound for children, who require smaller grafts. To alleviate the lack of available organs for young recipients, reduced[4] and then split[5] cadaveric liver transplants were performed in the 1980s. The scarcity of organs has been alleviated also in part by the development of live-donor liver transplantation (LDLT) programs in various centers.[6-9] This report reviews our experience with LDLT at the Hospital for Sick Children (Toronto, Ontario).

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MATERIALS AND METHODS

Overview of the Toronto Live-Donor Liver Transplant Program

The LDLT program in Toronto is a collaborative effort between the Toronto General Hospital and the Hospital for Sick Children. Donor evaluations, donor operations, and subsequent follow-up occurred at the Toronto General Hospital. Pediatric recipient operations and postoperative follow-up was at the Hospital for Sick Children.

At the time of liver transplant listing, parents were provided with information on LDLT. Prospective donors must self refer, and the evaluation protocol was guided by the principles articulated by the American Society of Transplant Surgeons.[10] Prospective donors were informed of their right to terminate evaluation at any stage in the process. All recipients had to be eligible to receive a cadaveric transplant and were maintained on the cadaveric transplant list up until they underwent LDLT.

Surgical Aspects of Pediatric LDLT

In the recipient hepatectomy, the vena cava was preserved, and the portal structures were divided beyond the bifurcation to provide maximal length for the anastomoses. Vascular anastomoses were performed using magnification or a microsurgical technique.[11,12] Arterial and portal venous reconstruction was achieved using native vessels. Biliary drainage was established with a Roux-en-Y hepaticojejunostomy or duct-to-duct anastomosis in cases of patients with short gut syndrome.

If primary closure of the abdominal wall was not possible, delayed closure with a SILASTIC® (Dow Corning, Midland, MI) patch was performed. The patient then followed the usual postoperative protocol and was taken back to the operating room for abdominal wall closure when the abdomen could accommodate the graft.

Postoperative Management

Baseline immunosuppression consisted of dual therapy of tacrolimus and prednisone. Long-term oral tacrolimus was started at 0.2 mg/kg/d to achieved target trough level of tacrolimus between 12 and 15 μg/mL in the first month posttransplant and tapered to target level of 5 to 8 μg/mL at 6 months posttransplant. After a rapid taper of intravenous methylprednisolone in the first 5 postoperative days, oral prednisone was started at 0.3 mg/kg/d and tapered off over the first 6 months posttransplant. Gancylovir (5mg/kg/d) was used as prophylaxis against cytomegalovirus virus (CMV) and Epstein-Barr virus (EBV) unless both the donor and recipients were EBV negative. To reduce thrombotic complications, recipients received heparin (50 to 100 U/h) and dipyridamole (3 to 6 mg/h) intravenously until they were able to tolerate oral acetylsalicylic acid (3 to 5 mg/kg/d). Liver ultrasound scan with hepatic artery Doppler was performed on the first postoperative day.

Data and Analysis

Approval for this study was obtained from the ethics review board at the Hospital for Sick Children. The hospital charts, transplant clinic charts, and transplant clinic electronic database were reviewed for all children who underwent a liver transplant from a live donor from the inception of our live-donor program in 1996 to March 31, 2002. Demographic data, indications for transplantation, and postoperative complications were collected for each patient from the time of transplant until March 31, 2002. These data were entered into a Microsoft Access database, and descriptive statistics were computed. For the purpose of analyses, complications were classified as major and minor. Major complications were those that were deemed to be a threat to either graft or life. All other complications were classified as minor.

RESULTS

Thirteen children (7 boys, 6 girls) received a LDLT during the index time period. One of the transplants was performed in 1996, and the remainder took place after the inception of our combined adult/pediatric LDLT program in 1999. Demographic data for the recipients and their donors is presented in Table 1. All donors were parents with the exception of one cousin. Pediatric recipients were between the ages of 4 months and 17 years (mean, 3.6 years). The indications for transplantation are listed in Table 1. There were no intraoperative complications. Ten (77%) children received a left-lateral segment graft, 2 (16%) received a right-lobe graft, and one (8%) child received a left-lobe graft. Three patients required placement of a SILASTIC® patch for abdominal wall closure. In one patient, graft torsion necessitated the urgent placement of a SILASTIC® patch on the second day posttransplantation. Delayed abdominal wall closure was achieved in 2 of these patients at 20 and 66 days posttransplantation. The remaining patient was 61 days posttransplantation at the time of this review with an intact SILASTIC® patch.

Table 1. Demographic Data

Donors	
Mean age at operation	34 yr
Relationship to recipient	
Mother	7
Father	5
Cousin	1
Recipients	
Mean age at transplantation	3 yr 7 mo (range, 4 mo-17 yr)
Male	7
Female	6
Mean weight at transplantation	16.1 kg (range, 5.5-54 kg)
Indications for transplantation	
Biliary atresia	9
Primary sclerosing cholangitis	1
Neonatal hepatitis	1
Total parenteral nutrition cholestasis	1
Acute fulminant hepatic failure not yet diagnosed	1

Table 2. Complications

Major complications	
Biliary complications	
Bile leak	2
Bile duct stricture	1
Major vascular complications	
Acute Budd-Chiari syndrome	1
Portal vein thrombosis	1
Other complications	
Lymphoproliferative disease	3
Post-operative bleeding	2
Bowel Perforation	1
Hemolytic anemia	1
Hemochromatosis from transfusions	1
Renal insufficiency	1
Volume overload/Cardiac failure	1
Total major complications	15
Total minor complications	31
Total complications	46

Forty-six complications occurred in 12 (92%) recipients (Table 2). The one patient who did not have a complication was only 6 days posttransplantation at the time of this review. On average, there were 3.53 complications per patient (1.15 major and 2.38 minor). Postoperative biliary complications included 2 (15%) biliary leaks and one (7%) biliary stricture. Both biliary leaks required laparotomy for repair. The biliary stricture was treated successfully with a percutaneous stent. The incidence of major vascular complications was 15%. One patient had acute hepatic venous occlusion after graft torsion on the second postoperative day. This was treated with a combined approach of surgery and interventional radiology with no graft loss.[13] Portal vein thrombosis occurred in one patient after splenectomy for hemolytic anemia 272 days posttransplant. Thrombolytic therapy was unsuccessful. The child remains well and still has no complications of portal hypertension. None of our patients had hepatic artery thrombosis. Ten (77%) patients experienced at least one episode of biopsy-proven acute rejection. The mean time from transplant to the first episode of rejection was 85 days. Five (39%) children

Table 3. Indications for Reoperation

Bile leak	2
Delayed abdominal wall closure	3
Bowel perforation	1
Splenectomy*	1
Postoperative hemorrhage	1
Planned relaparotomy/washout	1
Revision of T-tube	1
Tonsilectomy*	1

*Procedure performed during subsequent admission. All other operations performed during initial admission.

required an additional 12 operations after LDLT (Table 3). The average posttransplantation hospital stay for the first 11 patients who had been discharged was 36.5 days (range, 13 to 157 days). The remaining 2 patients were 6 and 61 days posttransplantation at the time of this review.

Ten of 12 initially EBV-negative patients became EBV positive after transplantation. Three of these patients had biopsy-proven posttransplant lymphoproliferative disorder (PTLD). In all cases, PTLD was diagnosed (128 to 257 days posttransplantation) at a stage of localized disease. All 3 patients were treated with gancyclovir, acyclovir, and cytogam. Two patients had their tacrolimus doses reduced, whereas one was converted from tacrolimus to sirolimus.

After discharge from the hospital, 8 (62%) children required 21 readmissions. The mean hospital stay per admission was 15 days (range, 1 to 182 days). The mean follow-up posttransplantation was 453 days with a median follow-up of 376 days (range, 6 to 2,112 days) during which graft and patient survival rate has been 100%.

DISCUSSION

Live-donor organ transplantation has been used as a strategy to deal with the chronic shortage of cadaveric renal grafts for the last 25 years. One of the major differences between kidney and liver transplantation is that liver transplantation is life saving, hence, a much stronger pressure on the potential donor to donate. The risk of liver donation on an otherwise healthy individual also is much higher, especially in right-sided donation. Those 2 points have raised many ethical concerns for the liver transplant teams involved. Fortunately, LDLT can be performed with acceptable donor morbidity.[9,14]

Since 2000, a total of 33 children have undergone liver transplantation at our hospital. There were 20 cadaveric and 13 live-donor liver transplants. Without the LDLT program, these children would have remained on the transplant waiting list, and some may have died of their disease. The 13 pediatric recipients of LDLT are all alive at a mean follow-up of 1.3 years.

In our series, 23% of the patients had biliary complications. Biliary complications are a source of significant morbidity in LDLT, occurring in 15% to 40% of patients.[15-17] The anastomosis is technically difficult because it is performed at the level of the right or left hepatic duct. Furthermore, ductal blood supply can be compromised during graft harvest.[18] This problem is compounded in children with short gut syndrome in whom duct-to-duct anastomosis is necessary to preserve bowel length. Well-drained drained leaks, in the absence of peritonitis, can be managed conservatively. Percutaneously dilated biliary strictures may recur and require biliary reconstruction for definitive management.[15,19,20]

Posttransplantation infection was the most common indication for readmission to hospital. Most infections were treated with appropriate antibiotic or antiviral therapies. As novel, targeted immunotherapies are developed, we expect that the frequency of these complications will be reduced.

PTLD continues to be a concern.[21] The mortality rate for this condition was reported initially to be as high as 60%.[22] Death often was caused by chronic rejection resulting from withdrawal of immunosuppression in an attempt to treat the PTLD. In more recent studies of children with primary tacrolimus-based immunosuppression, the incidence of PTLD was 13%, and the mortality rate from PTLD was 12%.[23] Twenty-three percent of our patients had biopsy-proven PTLD despite prophylactic gancyclovir therapy for primary EBV infection. All cases were diagnosed early. None of these patients died, and in all cases PTLD was easily treated with immunosuppression reduction and antiviral therapies.

Tight primary abdominal wall closure predisposes to hepatic vascular thrombosis, respiratory compromise, abdominal compartment syndrome, and wound dehiscence.[24,25] To avoid these complications, delayed closure of the fascia with temporary interposition of prosthetic material has been used.[25-27] This enables a child who cannot wait for a more size-matched donor to accommodate an oversized graft while waiting for hepatocyte apoptosis and recipient abdominal wall stretching. Three of our LDLT recipients required a SILASTIC® patch for abdominal wall closure. Other than the need to perform a second procedure to achieve final closure, no complications were directly related to using this technique.

LDLT can be performed with acceptable recipient morbidity and is an effective strategy to expand the donor pool. This is particularly relevant to the pediatric population in which appropriate-sized grafts are scarce. We expect that our LDLT program will grow over the next few years as we provide this lifesaving therapy to children with end-stage liver disease.

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