Transpl Int (2000) 13 [Suppl 1]: S150–S153

C. Margarit
M. Asensio
R. Dávila
J. Ortega
J. Iglesias
R. Tormo
R. Charco

Analysis of risk factors following pediatric liver transplantation

C. Margarit (✉) · M. Asensio · R. Dávila · J. Ortega · J. Iglesias · R. Tormo · R. Charco
Unidad de Trasplante Hepático, Hospital General Vall Hebrón, E-08035 Barcelona, Spain
Tel.: 34 93 2746113
Fax: 34 93 2746068

Abstract Several recipient, donor and operation factors as well as postoperative complications related to patient survival after liver transplantation (LT) in children were studied by univariate and multivariate analyses . In a 13-year period, 103 patients under 15 years of age underwent 120 LT; the mean age was 63 months and 36% were under 2 years of age. Indications for LT were cholestatic disease in 68 (56%), metabolic diseases in 18 (14%), fulminant hepatic failure in 8 (7.5%), cirrhosis in 7 (5.8%), and retransplants in 17 (14%). Whole liver was transplanted in 79% of cases and partial liver in 21%. Actuarial survival at 1, 5, and 10 years was 70%, 61%, and 57%, respectively. United Network of Organ Sharing (UNOS) I recipients (RR = 2.7), primary non-function (PNF) (RR = 13.9), and hepatic artery thombosis (HAT) (RR = 3.8) were independent factors for lower patient survival in multivariate analysis. Thus, in our experience, postoperative mortality as a consequence of the patient's condition before transplantation, or complications such as PNF or HAT, are the major causes of decreased survival in pediatric LT.

Key words Liver transplantation · Children · Risk factors for survival · Primary non-function · Hepatic artery thrombosis

Introduction

The purpose of this study was to present our 13 years of experience with 120 pediatric liver transplants (LT) and attempt to identify factors predictive of outcome.

Patients and methods

In a 13-year period (1985–1998), 103 children (49 girls, 54 boys; mean age 5.5 ± 4.1 years; range 0.5–15 years) received a total of 120 orthotopic liver transplants in our unit. Thirty-seven (36%) were under 2 years of age. Diseases requiring transplantation included cholestatic diseases (56%), metabolic diseases (14%), fulminant hepatitis (7.5%), and cirrhosis (5.8%); retransplantation was performed in 17 cases (15%) (Table 1). Only ABO-compatible livers were transplanted. Whole liver was transplanted in 79% of cases, reduced liver in 21%, and 4 were splits. Arterial anastomosis was performed with the recipient hepatic artery in most cases. However, when this artery was not suitable, an iliac graft was used in 25 cases or, as in our early experience, an aortic conduit in 6. Biliary drainage was established by duct-to-duct or, much more frequently, by a duct-to-Roux en Y small bowel loop. Primary immunosuppression with cyclosporine and steroids (88%) or tacrolimus and steroids (12%) was administered. The type and incidence of post-transplant complications were determined. Results were analyzed using Cox multivariate regression analysis to determine the statistical strength of independent associations between several variables and patient survival. The following variables were studied: recipient (age < 1 year, weight < 10 kg, indications, UNOS state, bilirubin > 10 mg%, prothrombin time < 60%, albumin < 2.5 g/l), donor (donor age < 12 months, etiology of brain death, whole or reduced graft, preservation time > 12 h, donor-recipient body weight ratio, DRBWR > 5), operation (intraoperative blood transfusion > 2 blood volume, type of arterial anastomosis), and post-transplant complications (primary non-function, PNF, hepatic artery thrombosis, HAT, portal vein thrombosis, postoperative infections, acute rejection, chronic rejection, post-

Table 1 Indications for liver transplantation

	n
Cholestatic liver disease	68
Biliary atresia	54
Paucity intrahepatic bile ducts	2
Familial cholestasis syndromes (Byler's disease)	4
Sclerosing cholangitis	6
Secondary biliary cirrhosis	2
Metabolic liver diseases	18
Alpha-1-antitrypsin deficiency	4
Tyrosinemia	4
Glycogen storage disease type I	6
Cystic fibrosis	2
Cholesterol ester storage disease	2
Fulminant liver failure	8
Hepatitis B	1
Amanita phalloides poisoning	1
Wilson's disease	1
Unknown origin	5
Chronic active hepatitis/cirrhosis	
Autoimmune	4
Hepatitis B cirrhosis	1
Cryptogenic cirrhosis	2
Miscellaneous	
Budd-Chiari	1
Neonatal hepatitis	1
Retransplantation	17
Primary non-function	5
Hepatic artery thrombosis	5
Acute rejection	2
Chronic rejection	5

transplant reoperation, retransplantation) (Table 2). Actuarial survival of patients and grafts was determined by the Kaplan-Meier method and compared using the log-rank (Mantel-Cox) test.

Results

Sixty-two (60.2%) patients are alive after a mean follow-up of 4.5 ± 4.2 years. Overall patient survival rates at 1, 5, and 10 years were 70%, 61%, and 57%, respectively, and the corresponding graft survival rates 60%, 51%, and 46%. Patient survival in the first period (1985–1991) was inferior to that in the second period (1992–1998): the 1 and 5-year actuarial patient survival was 65% and 73%, and 57% and 63%, respectively.

Post-transplant complications are presented in Table 2. PNF was the severest complication with 90% mortality; 4 patients died awaiting retransplantation and 5 were retransplanted, of whom only one survived. HAT was diagnosed in 11 patients, in the majority during investigations for biliary complications. These patients were treated with interventional radiology and/or surgical reconstruction of the bilioenteric anastomosis with a Kasai-like technique. Five patients with HAT were eventually retransplanted. Acute rejection was diagnosed and treated in 45% of patients, whereas 9.8% presented with chronic rejection and were treated with conversion from cyclosporine to tacrolimus, or retransplantation. Early mortality (before 3 months post-LT) was 27%. Sepsis (30%), multiorgan failure (MOF) (32%), and cerebral hemorrhage (16%) were the major causes of death during this period. Eight patients died more than 1 year after LT; recurrence of sclerosing cholangitis was an important cause of late mortality during this period.

Table 2 Post-transplant complications

Primary non-function	9 (7.5%)
Hepatic artery thrombosis	11 (9.1%)
Portal vein thrombosis	7 (5.8%)
Infection	74%
Acute rejection	45%
Chronic rejection	9.8%
Reoperation post-LT	22 (25%)

Univariate analysis revealed the following factors related statistically to patient survival (Table 3). Recipients under 1 year of age had a significant lower survival in our experience. Patients on the priority list for an organ owing to fulminant hepatic failure or urgent retransplantation, most of whom had multiorgan failure requiring ventilatory and hemodynamic support (UNOS 1), had a significantly decreased survival. Regarding indications for LT, metabolic diseases presented the best long-term survival, followed by biliary atresia. Fulminant hepatic failure and retransplantation had a significantly lower survival. Although no differences in survival rates were found between whole-organ and reduced grafts, patients also had lower survival when the donor recipient body weight ratio (DRBWR) was above 5. Requirements for blood transfusion superior to two blood volumes or the need for arterial anastomosis other than the classical form were factors related to decreased survival. Post-transplant complications such as PNF or vascular thrombosis were also significant factors for lower patient survival in univariate analysis.

Multivariate analysis showed that ICU treatment before LT (RR = 2.7), PNF (RR = 13.9), and HAT (RR = 3.8) were significant and independent factors for lower patient survival.

Discussion

Pediatric liver transplantation, despite undergoing a revolution over the last decade, remains a challenging therapy because of the scarcity of donor organs, complex surgical techniques required to accommodate a reduced liver in the recipient's abdomen, and the difficulties in post-transplant care. Advances in organ preserva-

Table 3 Risk factors for patient survival (*DRBWR* donor-recipient body weight ratio, *UNOS* United Network of Organ Sharing)

Factors	1 year (%)	5 years (%)	10 years (%)	*P*	RR
Recipient age					
< 1 year	54	18	18	0.006	
> 1 year	73	66	62		
Indications					
Cholestatic disease	78	63	60		
Metabolic disease	72	72	72		
Cirrhosis	57	57	57		
Fulminant hepatitis	50	37	18	0.016	
Retransplantation	44	39	26	0.002	
UNOS					
ICU	43	28	14		
Home	71	63	61	0.0027*	2.7
Whole-liver graft	69	60	56		
Reduced liver graft	60	60	60	NS	
Split	33				
DRBWR > 5	25	25		0.03	
Arterial anastomosis					
Classical	74	65	63		
Iliac conduit	40	40	40		
Aortic conduit	66	50	50	0.03	
Blood transfusion					
< 2 vol.	73	68	62		
> 2 vol.	53	38	38	0.03	
Primary non-function	11	11	11	0.0001*	13.9
Hepatic artery thrombosis	27	27		0.0004*	2.8
Portal vein thrombosis	43	43		0.012	

* Significant and independent factors related to patient survival in multivariate analysis

tion, surgical techniques, and pre- and postoperative care have permitted the rapid development of pediatric LT as a consequence of the great improvement in patient survival and quality of life [1–3]. The introduction of reduced and split liver techniques and finally living-related donor liver transplants, have permitted the donor pool to be expanded, thereby producing a significant decrease in the pretransplant mortality rate [4].

The probability of survival for 8 years after initial pediatric LT in the USA is 71% (58% without retransplantation) as shown by the Pitt-UNOS LT Registry [5]. Independent risk factors for survival among children included age, race, location awaiting transplantation, primary liver disease, serum creatine, and pre-LT bilirubin donor age. In patients with fulminant hepatic failure, Goss et al. [6] found that a recipient age of less than 4 years and ventilator dependency were independently and significantly correlated with patient survival. HAT occurs more frequently in pediatric than adult LT [3]; however, its incidence is declining due to refinements in surgical technique and the use of microvascular surgery [7], and antiaggregative therapy is also recommended. Portal vein thrombosis is also more frequent in children (incidence 2.2%–15%) ; risk factors include age, weight, small portal vein and emergent LT [8].

Survival after liver retransplantation is significantly decreased [3, 9]. This is not surprising, since the majority of patients present with multiorgan failure and require intensive care treatment prior to retransplantation. The possibility of obtaining a size-matched donor, on an urgent basis, is very remote.

The preoperative status of the patient does influence the outcome. Patients with metabolic liver diseases are usually in good nutritional and physiological condition and have the best long-term survival, whereas those with acute liver failure who require intensive care management, are in hepatic coma, and often have renal failure have a worse survival. Patients with biliary atresia are usually nutritionally compromised and have undergone previous surgery, but their survival rate approaches that of the total group. Pretransplant UNOS status has a great influence on survival, and recipients requiring ICU therapy prior to LT have a poorer outcome.

Recipient age contiues to be an important factor: Patients under 1 year old in our experience and that of others [3, 5] have poorer prognosis. They are usually biliary atresia patients after a failed Kasai operation, their nutritional status is poor and ascites, portal hypertension, and cholangitis are frequent complications; therefore, pretransplant mortality remains high. Reduction tech-

niques, split or live donations are necessary to be able to transplant these patients.

In our experience, the main causes of failure were PNF and HAT since most of these patients required urgent retransplantation. This procedure could only be performed with available livers from adult, frequently old donors and DRBWR of more than 5. Large graft reductions or splitting were necessary. The outcome of these complex surgical procedures performed in patients in very poor condition has been very poor.

In conclusion, postoperative mortality secondary to the condition of the patient before LT or post-transplant complications such as PNF and HAT are, in our experience, the major causes of decreased survival in pediatric patients undergoing LT.

References

1. Talbot D, Achilleos OA, Gunson BK, Beath S, Kelly DA, Buckels JAC, Mayer AD (1997) Progress in pediatric liver transplantation – The Birmingham Experience. J Pediatr Surg 32: 710–713
2. Andrews W, Sommerauer J, Roden J, Andersen J, Conlin C, Moore P (1996) 10 years of pediatric liver transplantation. J Pediatr Surg 31: 619–624
3. Goss JA, Shackleton CR, McDiarmid SV, Maggard M, Swenson K, Seu P, Vargas J, Martin M, Ament M, Brill J, Harrison R, Busuttil RW (1998) Long-term results of pediatric liver transplantation: an analysis of 569 transplants. Ann Surg 228: 411–420
4. Otte JB, Ville de Goyet J de, Reding R, Van Obbergh, Veykemans F, Carlier MA, Kock M de, Clement de Clety S, Clapuyt P, Sokal E, Lerut J, Delbeke I, Dierick V, Janssen M, Rosati R, Libert F (1998) Pediatric liver transplantation: from the full-size liver graft to reduced, split and living related liver transplantation. Pediatr Surg Int 13: 308–318
5. Belle SH, Beringer KC, Detre KM (1996) Recent findings concerning liver transplantation in the United States. Clin Transplant: 15–29
6. Goss JA, Shackleton CR, Maggard M, Swenson K, Seu P, McDiarmid SV, Busuttil RW (1998) Liver transplantation for fulminant hepatic failure in the pediatric patient. Arch Surg 133: 839–846
7. Mori K, Nagata I, Yanagata S, Sasaki H, Nishizawa F, Takada Y, Moriyasu F, Tanaka K, Yamaoka Y, Kumada K, Kikuchi H, Ozawa K (1992) The introduction of microvascular surgery to hepatic artery reconstruction in living-donor liver transplantation – its surgical advantages compared with conventional procedures. Transplantation 54: 263–268
8. Chardot C, Herrera JM, Debray D, Branchereau S, De Dreuzy O, Devictor D, Dartayet B, Norwood P, Lambert T, Pariete D, Gauthier F, Valayer J (1997) Portal vein complications after liver transplantation for biliary atresia. Liver Transpl Surg 3: 351–358
9. Newell KA, Millis JM, Bruce DS, Woodle ES, Cronin DC, Loss G, Grewal H, Alonso EM, Dillon JJ, Whitington PF, Thistlewaite JR Jr (1998) An analysis of hepatic retransplantation in children. Transplantation 65: 1172–1178