Outcome of liver transplantation for children with liver disease

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ABSTRACT

Introduction: The advent of liver transplantation has revolutionised the outcome of children with both acute liver failure and chronic end-stage liver disease. The aim of this study was to review the outcome of all paediatric liver transplants performed since the National Liver Transplant Programme began in 1990.

Methods: A retrospective review of all paediatric liver transplants from 1990 to December 2004 was performed.

Results: 46 liver transplants were performed in 43 children, of whom 23 (53.3 percent) were female. Median age at transplant was 21 months (range 11 months to 14 years). The most common indication for liver transplant was biliary atresia (71.7 percent). Living-related transplants accounted for 63 percent (29). Re-transplant rate was 6.5 percent with allograft loss as a result of hepatic artery thrombosis (two) and hepatic vein thrombosis (one). Tacrolimus was the primary immunosuppressive agent used in 89 percent of patients, with a 19.6 percent incidence of acute allograft rejection within the first six months. There were nine deaths. They were related to portal vein thrombosis (three), chronic rejection (one), sepsis (two), post-transplant lymphoproliferative disease (two) and primary graft non-function (one). Overall actuarial one- and five-year survival rate was 85.7 percent and 81.8 percent, respectively.

Conclusion: Liver transplantation is an established form of intervention for end-stage liver disease and a variety of liver-related metabolic disease. Our results are comparable to those of well-established liver transplant centres.

Keywords: biliary atresia, end-stage liver disease, liver transplantation, living-related transplant, paediatric liver transplant

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INTRODUCTION

The advent of liver transplantation has revolutionised care of children with end-stage chronic liver disease or acute liver failure. Unlike patients with chronic or acute renal insufficiency, patients with liver disease in the past had no option for long-term "liver-replacement" therapy. In 1981, the National Institutes of Health (NIH)[1] recognised liver transplantation as an accepted therapeutic option and no longer an experimental procedure. In Singapore, the first paediatric liver transplant was performed in 1991. The aim of this article is to review our 14-year experience in paediatric liver transplantation.

METHODS

The paediatric liver transplant programme is part of the National Liver Transplant Programme. The latter comprises a multidisciplinary team that meets once to twice per week to assess new patients who have been referred for liver transplant and to review patients on the waiting list or who have already received liver transplants. In addition, the paediatric team meets monthly to review children already on the list or post-transplantation.

Indications for liver transplantation in children include: (1) Decompensated liver disease with a known underlying progressive liver condition. (2) Acute liver failure meeting standard King's College criteria[2]. (3) Liver-based metabolic liver disease with no significant extrahepatic involvement. (4) Liver cancer (hepatoblastoma/hepatocellular carcinoma) with no extrahepatic spread. In the last few years, the National Liver Transplant Programme has implemented the use of the MELD and PELD scoring system as a measure for listing of adult and paediatric transplant patients, respectively[3]. This is in line with internationally-accepted liver transplant listing criteria.

Table I. Underlying pathological conditions that require liver transplantation.

Disease	Singapore	KCH, UK* (1989-2001)
	n=44 (%)	n=500
Biliary atresia	31 (70.5%)	32%
Other cholestatic liver disease eg paucity of intrahepatic bile ducts	5 (11.4%)	17%
Metabolic liver disease	3 (6.8%)	18%
Acute liver failure	2 (4.5%)	19%
Re-transplant	3 (6.8%)	14%

* King's College Hospital (KCH), United Kingdom, one of the largest paediatric liver transplant units in the world (personal communication).

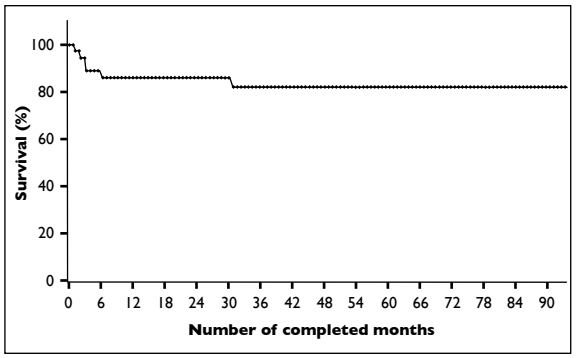

Fig. 1 Patient survival following liver transplant.

Table II. List of surgical complications encountered.

Event	n=28	Overall (%)
Biliary		
- Simple perihepatic collection (percutaneous drainage)	2	
- Biliary-enteric dehiscence	3	
- Persistent biliary collections (surgical drainage)	3	
- Biliary stricture	1	
	9	19.6
Vascular		
- Hepatic artery thrombosis	2	
- Hepatic vein thrombosis	1	
- Portal vein thrombosis	7	
	10	21.7
Others		
- Postoperative bleeding	2	
- Intestinal perforation	2	
- Intestinal obstruction	2	
- Wound dehiscence	1	
- Ventral hernia	2	
- Multiple abdominal wound sinuses	1	
- Intra-abdominal abscesses	1	
	11	23.9

This was a retrospective review of our experience in paediatric liver transplantation in Singapore, with particular reference to patient outcomes following transplantation, complications faced and causes of mortality. Patient data was analysed where appropriate, using the Statistical Package for Social Sciences (SPSS) version 10.0 (Chicago, IL, USA). Actuarial survival was estimated with Kaplan-Meier analysis.

RESULTS

There were 46 liver transplants in 43 children, 23 (53.5%) of whom were female. Median age at transplant was 21 months (range, 11 months to 14 years). Indications for liver transplant are shown in Table I, with biliary atresia being the single most common cause of end-stage liver disease (n=31, 70.5%). The liver allograft was from a living-related donor in 63% of the liver transplants (73% of whom were the child's mother). Since the introduction of living-related liver transplantation in 1996, overall waiting list mortality was 22% (n=13, of which three were from acute liver failure). In patients without suitable living donors, mortality rate while awaiting a cadaveric organ was 63%, as compared to 5% where a living donor was present.

Overall actuarial one- and five-year survival was 85.7% and 81.8%, respectively (Fig. 1), with no significant difference between recipients of cadaveric grafts or living-related transplants (p=0.05). Causes of mortality include primary non-function (1), portal vein thrombosis (3), lymphoproliferative disease (2), sepsis (2) and chronic rejection (1). All survivors except three were able to return to age-appropriate education and activities. These three children required special education. One child had underlying glycogen storage disease with a pre-transplant IQ of 70. A second child sustained hypoxic encephalopathy pre-transplant with good motor recovery but has residual behavioural problems. The third child was diagnosed with attention deficit hyperactivity disorder (post-transplant).

All patients experienced at least one complication postoperatively, either directly related to surgery or to the use of immunosuppressive therapy, usually within the first six months of transplant. The main medical complications include allograft rejection, infection and immunosuppression related side-effects such as tremors and hypomagnesaemia. Surgical complications include vascular thrombosis, biliary tract problems and bowel perforation (Table II). Primary immunosuppressive therapy, which is the

Table III. Infections in paediatric liver transplant recipients.

Site/type of infection	n	Overall (%)
Respiratory tract	23	50
Drain/intra-abdominal	23	50
Wound	8	17.4
Bacteraemia	8	17.4
Significant viral infections		
Cytomegalovirus	5	10.9
Ebstein Barr virus	6	13

current standard immunosuppressive protocol of the unit, comprised tacrolimus and prednisolone in the majority (89%). Acute allograft rejection within the first six months of transplant occurred in nine patients (19.6%). All except one were steroid responsive.

There were a total of 38 infectious episodes in the 46 liver transplants, and infection was the direct/contributing cause of death in four. The sites/sources of infections are shown in Table III. Respiratory tract infection was determined to be present if there were clinical and radiological appearance of infection, with or without the presence of positive respiratory cultures (endotracheal aspirates), and antibiotics were used to treat the episode. Intra-abdominal infection was defined as the presence of an intra-abdominal collection that required anti-microbial treatment, interventional drainage, or was associated with positive bacterial cultures.

Cytomegalovirus (CMV) and Epstein Barr virus (EBV) were the two viral infections that contributed to significant patient morbidity and mortality. Almost half of all paediatric recipients were CMV-negative (n=22) at the time of transplant, the majority of whom received CMV-positive allografts (n=20). CMV disease was seen in five children, involving the allograft (hepatitis) or colon (colitis). Ganciclovir prophylaxis was used from 1997, with a significant reduction in the incidence of post-transplant CMV disease from 50% to 7.6%. EBV infection was seen in six children, presenting initially with flu-like symptoms and progressing to post-transplant proliferative disease (PTLD). PTLD was the direct cause of death in two children, and these occurred in the first few years of the programme.

In our series, vascular complications were encountered in ten (21.7%) patients, portal vein thrombosis in seven, hepatic vein thrombosis in one, and hepatic artery thrombosis (HAT) in two. Of these children, four died as a direct consequence of the portal hypertension and its complications, two are alive and well following meso-caval shunting, and three have received re-transplants – one because of intractable Budd Chiari syndrome (the child with hepatic vein thrombosis) and two for persistent hepatic sepsis (secondary to HAT). One child died of PTLD and portal vein thrombosis was found incidentally on post-mortem examination.

DISCUSSION

The overall survival of children following liver transplant locally is similar to those reported in overseas centres. Current one-year survival for children undergoing liver transplantation for chronic liver disease in Europe or North America is 80-90% compared to a figure of 30% in the late 70's[4,5]. This is mainly due to advances in immunosuppressive therapy and improvements in surgical techniques. Data from Asian centres are not significantly different. A recent Hong Kong series reported that patient and graft survival after a median follow-up of 38 months (range 1-96 months) was 79% and 74%, respectively[6], while in Taiwan (n=13), the actuarial patient and graft survival at two years was 92%[7].

However, the use of potent immunosuppressive agents has resulted in a number of infectious complications that may be associated with significant patient morbidity and mortality[8]. The reported rates of infection following liver transplantation are between 47% and 80%, with a mean of one to 2.5 episodes of infections per patient[9,10]. An understanding of individual patient risk characteristics and the use of prophylactic anti-microbial agents where appropriate (such as ganciclovir for CMV disease) have enabled us to limit these infectious complications to some extent.

Vascular thromboses following liver transplantation continue to be a significant cause of graft loss and patient morbidity, and have a higher incidence in the paediatric transplant recipient compared to their adult counterparts. This is partly due to their smaller vascular size, and this has been minimised in recent years with the use of microsurgical techniques. Our local experience is similar to those reported internationally, where the incidence of HAT is seven to 17%[11,12], and that of portal vein thrombosis as high as 33%[13]. Roux-loop hepaticojejunostomy is the commonest biliary drainage procedure in paediatric liver transplantation compared to duct to duct anastomosis in adults. Biliary complications occur in approximately 10-20% of paediatric transplant recipients[14-16]. These include biliary leaks, anastomotic strictures and intrahepatic strictures. The expertise of an interventional radiologist in the evaluation and therapeutic intervention is essential[17]. This is particularly important for biliary

strictures where percutaneous transhepatic dilatation is usually required. Occasionally, the combined management of the interventional radiologist and endoscopist is needed, as was in our own experience of an anastomotic biliary stricture in one child.

One of the major limitations in paediatric liver transplantation has been the lack of suitable size-matched organs. Advances in surgical techniques to allow reduced-size grafts and living-related donation have resulted in reduced waiting list mortality[18,19], and this is our local experience following the development of the living-related liver transplant programme. At the same time, initiatives to increase cadaveric organ donation continue to be a challenge. The recent changes to the human organ transplant act are but one of the means to do so.

Liver transplantation has progressed in the last two decades from an experimental procedure to one that is a recognised cure for a variety of liver diseases. Overall survival is good. The current goals are for tailored immunosuppression in order to limit morbidity associated with the longer-term use of immunosuppressive agents, and looking beyond survival to issues, such as quality of life, as important end-points.

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