Liver transplantation at Red Cross War Memorial Children's Hospital

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The liver transplant programme for infants and children at Red Cross War Memorial Children's Hospital is the only established paediatric service in sub-Saharan Africa. Referrals for liver transplant assessment come from most provinces within South Africa as well as neighbouring countries.

Patients and methods. Since 1987, 81 children (range 6 months - 14 years) have had 84 liver transplants with biliary atresia being the most frequent diagnosis. The indications for transplantation include biliary atresia (48), metabolic (7), fulminant hepatic failure (10), redo transplants (3) and other (16). Four combined liver/kidney transplants have been performed. Fifty-three were reduced-size transplants with donor/recipient weight ratios ranging from 2:1 to 11:1 and 32 children weighed less than 10 kg.

Results. Sixty patients (74%) survived 3 months - 14 years post transplant. Overall cumulative 1- and 5-year patient survival figures are 79% and 70% respectively. However, with the introduction of prophylactic intravenous ganciclovir and the exclusion of hepatitis B virus (HBV) IgG core Ab-positive donors, the 1-year patient survival is 90% and the projected 5-year paediatric survival is > 80%. Early (< 1 month) post-liver-transplant mortality was low. Causes include primary malfunction (1), inferior vena cava thrombosis (1), bleeding oesophageal ulcer (1), sepsis (1) and cerebral oedema (1). Late morbidity and mortality was mainly due to infections: *de novo* hepatitis B (5 patients, 2 deaths), Epstein-Barr virus (EBV)-related post-transplantation lymphoproliferative disease (12 patients, 7 deaths) and cytomegalovirus (CMV) disease (10 patients, 5 deaths). Tuberculosis (TB) treatment in 3 patients was complicated by chronic rejection (1) and TB-drug-induced subfulminant liver failure (1).

Conclusion. Despite limited resources, a successful paediatric programme has been established with good patient and graft survival figures and excellent quality of life. Shortage of donors because of infection with HBV and human immunodeficiency virus (HIV) leads to significant waiting-list mortality and infrequent transplantation.

S Afr Med J 2006; **96:** 960-963.

The liver transplant programme for infants and children at Red Cross War Memorial Children's Hospital is at present the only established paediatric service in sub-Saharan Africa. The first paediatric transplant was performed on 6 December 1987 for end-stage liver disease due to alpha-1-antitrypsin deficiency. The patient unfortunately died of complications in January 1988. The paediatric programme was then put on hold until the adult programme had become established at Groote Schuur Hospital and was restarted in November 1991.[1] Referrals for liver transplant assessment come from most provinces within South Africa as well as neighbouring countries.

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Patients and methods

Since 1987, 84 orthotopic liver transplants have been performed on 81 children and all are included in this retrospective review. The major indication for liver transplantation was biliary atresia (57%) followed by acute liver failure (12%). There were 4 combined liver/kidney transplants for primary hyperoxaluria (3) and congenital hepatic fibrosis associated with polycystic kidneys (1).

Demographics. The age of the children ranged between 6 months and 14 years (mean 4.6 years) and included 38 male and 43 female children. The racial distribution was as follows: 14 black, 33 mixed race, 4 Asian and 30 white. Their weight ranged between 4 kg and 50 kg (mean 13 kg) and 32 children weighed < 10 kg.

Indications for liver transplantation. The indications for liver transplantation are listed in Table I.

Surgical techniques. The surgical techniques used for donor retrieval and recipient liver removal and engraftment have

Table I. Indications for liver transplantation

Biliary atresia		48
Fulminant hepatic failure		10
Metabolic		7
Alpha-1-antitrypsin deficiency	4	
Primary hyperoxaluria	3	
Redo transplants		3
Chronic rejection	2	
Acute rejection	1	
Other		16
Autoimmune hepatitis	6	
Cryptogenic cirrhosis	2	
Neonatal hepatitis	3	
Budd-Chiari syndrome	1	
Alagille syndrome	2	
Congenital hepatic fibrosis	1	
Hepatoblastoma	1	

been previously described in detail.[1-3] Fifty-three reduced-size grafts were used (31 left lateral segment, 18 left lobe, 4 right lobe). In all the reduced-size livers and in patients with biliary atresia, choledochojejunostomy was used for biliary drainage without the use of stents or T-tubes. The donor: recipient weight ratios varied between 2:1 and 11:1 (mean 3.4:1.) One living related (mother-child) transplant was performed.

Anaesthesia. The anaesthetic time ranged from 7 to 16 hours (mean 9 hours) and the mean blood volume transfused was 2.5 blood volumes (range 0.5 - 5.7). Blood-group crossmatch was identical in 66, compatible in 16 and incompatible in 2 cases.

Immunosuppression. Baseline immunosuppression consisted of triple therapy in the form of cyclosporin, methylprednisone and azathioprine. Oral cyclosporin (5 mg/kg) was given immediately prior to surgery and continued postoperatively initially intravenously, but since 1997 it has been given orally, using Neoral cyclosporin 3 times a day aiming for a trough level of 350 - 400 ng/ml initially and a 2-hour peak level greater than 1 000 ng/ml.[4] Methylprednisolone (10 mg/kg) and azathioprine (0.5 - 1 mg/kg) was given intravenously at the time of reperfusion of the graft and the methylprednisolone dosage was reduced in the first week to 1 mg/kg for the first month and then further reduced to 0.2 mg/kg as maintenance. Azathioprine was continued for approximately 6 months. Rejection episodes were managed with 3 - 4 daily pulses of methylprednisolone, but increasingly this has not been required with early conversion to tacrolimus and selective use of mycophenolate mofetil. Recently anti-CD25 antibodies have been used (basiliximab at 20 mg/dose for weight > 40 kg, 10 mg/dose for weight < 20 kg; daclizumab 1 mg/kg/dose) both used as a 2-dose regimen.[5] Rapamycin has also been used in two patients with chronic rejection, high Epstein-Barr virus (EBV) levels and associated post-transplant lymphoproliferative disease (PTLD).

Infection prophylaxis.[6-10] Intravenous ampicillin and cephalosporin is given at anaesthestic induction, repeated together with metronidazole at the time of biliary anastomosis and continued for 3 - 5 days peri-operatively. Antifungals in the form of oral mycostatin and amphotericin lozenges are given, and patients with severe cholestasis and prolonged pre-transplant inpatient treatment receive intravenous amphotericin peri-operatively for ± 2 weeks. Co-trimoxazole 6 mg/kg/day in 2 divided doses is given 3 days/week for prevention of *Pneumocystis carinii* infection and is continued for 6 months. Intravenous ganciclovir 5 mg/kg twice daily was given as viral prophylaxis against cytomegalovirus (CMV) and EBV infections, initially for 2 weeks, but since 1996 this is given for 3 months in children under the age of 3 and in high-risk children not previously exposed to EBV in an attempt to prevent PTLD.[11] In addition, Polygam is given intravenously for the first 5 days post transplant and all blood products are leucocyte filtered. TB prophylaxis is used in high-risk patients only.

Results

Since 1987, 84 orthotopic liver transplants have been performed on 81 children. All patients have survived the procedure and currently 60 (74%) patients have survived 3 months to 14 years post transplant. Fifty-one children have an excellent quality of life.

The causes and timing of death are as follows: (*i*) *early (≤ 1 month):* sepsis (1), bleeding oesophageal ulcer (1), primary non-function (1), inferior vena cava (IVC) thrombosis (1), cerebral oedema (1); (*ii*) *intermediate (> 1 - 6 months):* rejection and associated sepsis (1), portal vein thrombosis with variceal bleed (1); (*iii*) *late (> 6 months):* bacterial, viral and fungal infections (5), PTLD (7), chronic rejection (2).

Surgical complications

Hepatic artery thrombosis occurred in 2 patients and portal vein thrombosis in 6 patients. Four patients developed early portal vein thrombosis (< 6 months). In 2 patients, the portal vein thrombosis was successfully repaired and the third presented with an uncontrollable variceal bleed 6 months post transplant. Attempts at a Meso-Rex shunt and redo portal anastomosis failed in the fourth patient who remains clinically stable on enoxaparin sodium (Clexane) therapy. Two late portal vein thromboses occurred (> 1 year) resulting in portal hypertension and recurrent GIT bleeds. They were managed successfully with a Meso-Rex shunt. IVC thrombosis occurred in 2 patients and this was treated with thrombolytic therapy, which was successful in 1 patient (6 months post transplant), but the second patient died from bleeding and sepsis in the peri-operative period. Bile leaks occurred in 4 patients; in 2 these were successfully managed with revision of the biliary anastomosis and in the other 2 patients, the biliary leak was associated with a reduced-size graft and settled

spontaneously. Four patients developed postoperative GIT bleeding. Two required relook laparotomies, with the revision of Roux-en-Y anastomosis in 1, while the other patient was noted to have bleeding from the cut-surface of liver, which was cauterised. One patient's postoperative GIT bleeding settled spontaneously, and another patient presented with uncontrollable bleeding from a postsclerotherapy oesophageal ulcer.

Medical complications

Tuberculosis (3). Two children developed pulmonary tuberculosis and 1 patient a pleural effusion. TB drug treatment was complicated by chronic rejection in 1 patient and TB-drug-induced subfulminant liver failure in 1 patient.

***De novo* hepatitis B (5).** Hepatitis B virus infection is endemic in South Africa with an HBsAg incidence of 3 - 20% and a HB IgG core Ab incidence of 40 - 80%. Forty per cent of the potential donors are HB IgG core Ab-positive. Prior to 1996, donors were only screened for HBsAg. Five children (6 - 14 months post transplant) developed *de novo* hepatitis B. All had been HBsAg-negative pre-transplant and the explanted liver showed no evidence of hepatitis B infection. Three of the children had received organs from Hep B IgG core Ab-positive donors and sera was not available for testing in 2. Two children have developed mild chronic hepatitis and 2 have developed severe chronic hepatitis progressing to cirrhosis. The DNA levels ranged between 1 920 and 4 800 pg/ml (mean 3 556 pg/ml). All patients were treated initially with famciclovir and then changed to lamivudine.[12-14] Lamivudine resistance developed in 2 patients and 2 have died as a result of progressive chronic hepatitis B and complications of cirrhosis. One died soon after diagnosis from TB-drug-induced liver failure.

CMV infection and disease. CMV infection is endemic in our population and 90% of donors were CMV-positive.[15] CMV infection as defined by the presence of fever together with a positive culture or positive pp65Ag occurred in 12 patients and was treated successfully with intravenous ganciclovir. Ten patients developed CMV disease and the sites of disease included the lung (4), liver (7), pancreas and GIT (1). Five of the 10 patients with CMV disease have died. Risk factors for CMV infection and disease include poor nutritional status, high-dose steroids and pulsing. Since 1995, the regular use of CMV pp65Ag monitoring has enabled earlier diagnosis and treatment of CMV infection and consequently less disease. At present pre-emptive intravenous ganciclovir is given to all high-risk children and this has contributed to a decrease in the incidence of CMV disease.

EBV and PTLD (12). EBV infection has resulted in significant morbidity and mortality in our children. Twelve children developed PTLD (all of them < 3 years of age) and the mean time to development of PTLD was 9.2 months (range 3 - 30 months post transplant). Eight had typical acute membranous tonsillitis with associated lymphadenopathy. Seven children were EBV nuclear antigen (EBNA)-positive at time of transplant and all were positive at time of diagnosis of PTLD. Sites of involvement include tonsils (8), intestine (6), mediastinum (4) and CNS (4). On histology, there were 6 monoclonal, 2 oligoclonal and 4 polyclonal PTLD. Management of PTLD included the reduction of immunosuppression in all patients with complete withdrawal in 2 patients.[10-11] Adenotonsillectomy was performed in 7 patients and debulking surgery in 4. Of the 3 patients who received chemotherapy, all died within 10 weeks of diagnosis. Two patients have received intravenous rituximab. Seven patients died as a result of PTLD and 1 required a retransplant for chronic ductopenic rejection. Overall there was a 15% incidence of PTLD in our programme with a 58% mortality, despite the use of chemotherapy, reduction in immunosuppression and rituximab therapy.

Survival

The overall cumulative 1-year and 5-year patient survival is 70% and 79% respectively. Since 1996, with the introduction of IVI ganciclovir for 3 months and the exclusion of HBV IgG core Ab-positive donors, the 1-year patient survival is 90% and the projected 5-year survival is > 80%.

Discussion

As the only established paediatric liver transplant centre within South Africa, children are referred from all over South Africa. In the early stages of our programme, children were referred in a pre-morbid clinical state and frequently died while awaiting a liver transplant. However, with increasing public awareness and education of the medical fraternity, children are now increasingly being referred early on in the course of their liver disease. Successful outcomes to liver transplantation however, are dependent on both a committed family and committed medical support, particularly when the child returns home to a medical centre in another province.

Endemic viral and bacterial infections, particularly TB, CMV, EBV and hepatitis B have had a significant impact on our programme[12,13,15-17] The recent ability to monitor CMV pp65 Ag and EBV polymerase chain reaction (PCR) has enabled us to recognise viral infections earlier, treat appropriately and decrease immunosuppression. The *de novo* hepatitis B in the 5 children was probably acquired as the result of using hepatitis B core Ab-positive donors.[18] Two children have died as a result of chronic hepatitis B and 2 have developed lamivudine resistance. Since 1996, hepatitis B IgG core Ab-positive donors have been excluded as potential liver donors and no further cases of *de novo* hepatitis B have occurred. The hepatitis B IgG core Ab-positive rate in the donor pool is approximately 40% and this together with the increasing prevalence of HIV has significantly decreased the number of potential donors.

With the introduction of aggressive antiviral prophylactic regimens and the exclusion of hepatitis B core Ab-positive donors since 1996, the predicted 5-year patient survival figures are now greater than 80%, which is comparable with other reported series. Despite limited resources, diminishing manpower and a decreasing donor pool, the Red Cross Children's Hospital paediatric liver programme continues to be active with survival figures comparable with large centres elsewhere. With increasing public awareness, the number of children requiring transplantation will increase and at present split liver transplantation is beyond the capacity of our restricted manpower. Other options that need to be considered in expanding the donor pool are the increasing use of marginal donors and embarking on an active living-related programme.

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Accepted 28 June 2006.