Transplant Int (1992) 5 [Suppl 1]: S 206–S 208

TRANSPLANT
International

Liver transplantation for fulminant liver failure in children

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Abstract. The mortality rate of fulminant hepatic failure (FHF) in childhood has remained between 70% and 95% despite recent improvements in medical therapy. Liver transplantation has become an important therapeutic option in adults with this entity, but has been infrequently performed in children. Many children do not receive transplants because of the rapid progression of the illness and the lack of suitable donor livers. We present our experience in liver transplantation in children with FHF. Between March 1988 and December 1989, seven children aged between 15 months and 12 years received eight liver transplants. The aetiology of FHF was viral hepatitis in five and drug hepatotoxicity (carbamazepine) in two. Five of our patients were in grade III–IV coma. Reduced-sized livers were used in six of the eight transplants. The postoperative morbidity included viral and fungal infections, and abdominal bleeding. Two patients died from graft-versus-host disease and one from brain aspergillosis. Four patients (57%) survived a median follow-up of 15 months. Liver transplantation should be the therapeutic option in children with FHF where the chances of medical recovery are poor.

Key words: Transplantation – Liver transplantation – Fulminant hepatic failure

Fulminant hepatic failure (FHF), an infrequent and catastrophic illness in children, is characterized by widespread necrosis of hepatocytes and is caused by a wide variety of hepatic insults. The condition, first defined by Trey and Davidson, requires the development of hepatic encephalopathy within 8 weeks of the onset of illness in an individual with no evidence of previous liver disease [18]. The mortality rate for this condition has remained between 70% and 95% despite recent improvements in medical therapy [6, 10, 15].

Liver transplantation is increasingly accepted as a treatment modality for FHF specially in adults [3, 9, 13, 19]. The experience in children is scarce, mainly because of the rapid evolution of the illness and the lack of paediatric donor livers.

We present our experience in liver transplantation in seven children with FHF.

Material and methods

From March 1988 to March 1991, 148 patients received 161 orthotopic liver transplants at King's College Hospital, of whom seven were children with FHF. There were four males and three females, with a mean age of 6 years (range 1–12 years). The causes of the FHF were acute viral hepatitis in five (four non-A non-B hepatitis, and one hepatitis A) and carbamazepine toxicity in two (Table 1).

Preoperative medical management included the correction of the coagulation disorders by plasma, cryoprecipitate infusion or exchange transfusion. Endotracheal intubation was instituted when patients had difficulty in controlling secretions or in grade IV encephalopathy. Intracranial pressure (ICP) was monitored in children with cerebral oedema. Mannitol and thiopentone infusions were used to reduce the intracranial pressure. The decision for transplantation was made according to 'The King's College Criteria' [11] which includes: age < 10, > 40 years; aetiology (non-A non-B hepatitis, and idiosyncratic drug reactions); jaundice more than 7 days; prothrombin time > 50 s; and serum bilirubin > 300 μmol/l (providing that no absolute contraindication for transplantation such as uncontrolled sepsis, cardiovascular instability or irreversible brain damage is present). Two children met three criteria, and five met four or more criteria for transplantation.

Six of the seven children presented with hyperbilirubinaemia (median 403 mmol/l, range 87–632), and transaminaemia (mean 1470 IU/l, range 144–6000). Hepatic encephalopathy was stage II in two, stage III in three and stage IV in two. All had severe coagulopathy as evidenced by prolongation of prothrombin time, with a mean value of 63 s (range 33–104 s). However, with the correction of the coagulopathy at the time of transplantation the prothrombin time decreased to a mean value of 16 s.

Orthotopic liver transplantation, and reduced-sized liver transplantation were performed according to accepted techniques [5, 17]. Veno-venous bypass was not used. Baseline immunosuppression was achieved with cyclosporin A (CsA), steroids and azathioprine.

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Table 1. Clinical and biochemical data of the seven children receiving transplants

Sex	Age (months)	Diagnosis	Bilirubin (mmol/l)	AST (IU/l)	Creatinine (mmol/l)	PT (s)	Coma grade	Ascites
F	72	Carbamazepine hepatotoxicity	507	1325	107	63	III	Yes
F	24	Carbamazepine hepatotoxicity	87	6000	91	87	III	Yes
M	48	NANB hepatitis	370	638	51	32	III	No
M	132	NANB hepatitis	632	776	106	104	IV	Yes
M	144	Hepatitis A	507	1325	107	63	III	No
F	84	NANB hepatitis	555	465	81	33	II	No
M	12	NANB hepatitis	389	144	62	48	II	Yes

NANB, non-A non-B hepatitis; AST, aspartate aminotransferase; PT, prothrombin time; Coma grade, encephalopathy grade

The dosage of CsA was adjusted according to daily radioimmunoassay levels to maintain a trough level of 150–200 ng/ml. Episodes of allograft rejection were treated with pulse doses of steroids.

Results

Liver transplantation was performed from 1 to 5 days (mean 3 days) after the patient was listed in the 'emergency' category with the UK Transplant Service. Eight liver transplants were performed in seven children; one child required retransplantation 6 months later because of severe biliary obstruction. Two patients received a full-sized graft; reduced-sized grafts were used in six, utilizing the left lateral segment in three and the left tobe in three (Table 2).

The operative procedure was technically simple because of the absence of portal hypertension and no previous abdominal operations. The presence of coagulopathy including fibrinolysis, resulted in mean blood losses of 1400 ml (range 515–4000 ml). The histology of the excised livers showed massive or submassive hepatocellular necrosis, bridging between portal tracts and central veins and portal tract inflammatory cell infiltrate.

Postoperative complications developed in five of the children. Acute rejection was diagnosed and treated in three. Abdominal bleeding was a problem in two (one required a laparotomy), fungal infection in two (disseminated candidiasis in one and brain aspergillosis in one), CMV pneumonitis in two, biliary obstruction and subhepatic abscess in one, and portal vein thrombosis in one who required a thrombectomy (Table 3).

Three children died during an observation period of 3 to 22 months. Two children developed graft-versus-host disease (GVHD). They were treated with high doses of steroids, antilymphocyte globulin and thalidomide. In both cases disseminated CMV infection was detected and treated with gancyclovir. Neither of them responded to anti-GVHD therapy, and died with disseminated infection. One patient developed brain aspergillosis and never responded to aggressive medical therapy.

Of the seven patients, four (57%) were alive at the time of writing. The median duration of follow-up was 15 months (3 months to 3 years). Neurological recovery in the survivors was complete.

Discussion

The criteria for selecting children with FHF who are suitable for liver transplantation remain difficult to establish. The decision has to be taken before the development of severe complications, such as cerebral oedema, hypoglycaemia, renal failure and sepsis. The decision for transplantation was taken for our children with the assistence of the King's College Criteria [11]. Using these criteria it has been shown that in patients with more than three factors present mortality without transplantation is up to 95%.

Once the decision for transplantation has been taken, the coagulopathy should be corrected with the administration of fresh frozen plasma, cryoprecipitate, platelets and exchange transfusions. If clinical signs of cerebral oedema are detected, the insertion of an extradural ICP monitor is advisable [14]. Episodes of raised ICP can be successfully managed with hyperventilation, hyperosmolar mannitol and thiopentone infusions.

The lack of suitable paediatric donor livers makes the use of reduced-sized and ABO-incompatible grafts neccessary. Four of our children received transplants across ABO blood group barriers. These grafts have previously been associated with an increased incidence of severe rejection, arterial thrombosis and cholangitis [7]. In the present series, no such association was demonstrated. Because of the possible complications, the use of ABO-incompatible grafts can only be recommended in emergency situations. Five of our grafts were reduced-sized grafts. It has been shown by others that graft and patient survival is the same in full-sized or reduced-sized grafts [12].

Table 2. Graft type and surgical complications

Patient	Graft type (segments)[a]	Complications
1	Standard	
2	II, III, IV.	
3	Standard	
4	II, III	Intraabdominal bleeding biliary obstruction
(R)	II, III	Subhepatic abscess
5	II, III	
6	II, III, IV	Intraabdominal bleeding
7	II, III, IV	Portal vein thrombosis

[a] Hepatic segments according to Couinaud; R, retransplantation

Table 3. Postoperative complications in the children transplanted

		Mortality
Acute rejection	3	
Pneumonia	3	
Intraabdominal bleeding	2	
Graft versus host disease	2	2
CMV infection	2	
Fungaemia	2	1
Biliary obstruction	1	
Portal vein thrombosis	1	
Subhepatic abscess	1	
Retransplantation	1	
		3 (42%)

Several defects in immunological function have been described in patients with FHF [1, 8, 21]. These defects, together with the use of invasive monitoring, immunosuppression, broad spectrum antibiotics, and treatment for graft rejection, render the child highly suceptible to bacterial and fungal infections [16, 20]. This appears to be reduced by the use of selective bowel decontamination. If sepsis is suspected the aggressive use of antibiotics and antifungals is recommended.

GVHD is a complication rarely seen after liver transplantation in adults, and few cases have been reported [2, 4]. Two of our cases developed GVHD, and both had received reduced-sized livers from an adult donor. Several factors may have been involved in the development of GVHD in these children. A relatively large pool of immunologically competent cells is grafted into a small host with defective immunological function which makes them incapable of mounting an effective response against transplanted lymphocytes. The results of treatment with CsA, increased doses of steroids, antilymphocyte globulin and thalidomide proved dissappointing.

The survival rate obtained so far with liver transplantation is encouraging (57%). In our experience, and in other adult centres, the survival rate in patients with FHF is significantly lower than for elective cases. To improve the results early referral of these children to centres with facilities and experience in liver transplantation is desirable. Better criteria for transplantation which identify early those children who will not survive without transplantation need to be developed.

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