Occasional Review

Current results with orthotopic liver grafting in Cambridge/King's College Hospital series

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Abstract

In the 12 months from 1 August 1983 to 31 July 1984, 29 orthotopic liver transplant operations were performed in 26 patients, 10 of whom were aged 20 or under. Results in this younger age group were very satisfactory, nine of the patients being alive at review, giving an actuarial predicted one year survival of 75%. In the older age group seven of the 16 patients were alive, perioperative bleeding and infection in association with malnutrition being major factors in the nine who died. Two patients in whom a blocked portal vein required disobliteration at the time of the operation made excellent recoveries. An increase in availability of donor organs made possible a greater use of retransplantation, and for the first time transplantation for severe liver failure due to subacute hepatic necrosis was successful.

Introduction

Following on from the final statement by the National Institutes of Health consensus development conference in June 1983 that "liver transplantation is a therapeutic modality for end stage liver disease that deserves broader application"¹ there has been a resurgence of interest in the procedure, with an increase in the number of centres carrying out liver transplantation and many more operations being done by established groups. In the Cambridge/King's College

Hospital programme, which began in May 1968 and in which 167 patients have been treated to date, there have been many changes in operative technique, selection of patients, and immunosuppressant drug regimens. This may make consideration of overall results alone misleading, Starzl and his colleagues showing in particular a very substantial improvement in survival rate since the introduction of cyclosporin A in 1980.² In this paper we report our experience during the 12 months up to 31 July 1984 and the excellent results being obtained in the younger age group.

Patients and methods

Between 1 August 1983 and 31 July 1984, 26 patients underwent liver transplantation, three of them receiving transplants on two occasions. The patients (cases OL142-167 in the Cambridge/King's College Hospital series) were divided into a young group of 10 patients (five male, five female) aged 2-20 years and an older one of 16 patients (six men, 10 women) with an age range of 36-58 years (table).

Of the four patients with biliary atresia, three had had Kasai operations before the age of 4 months. The fourth, aged 11 years (case OL153), was unusual in that his serum bilirubin concentration had remained only moderately raised. One patient in each age group had cirrhosis from α_1 antitrypsin deficiency (cases OL146 and 160), and the other patient with inborn error of metabolism (case OL163) was an 18 year old man with primary hyperoxaluria. This had resulted in calcium oxalate nephrolithiasis and chronic renal failure. A kidney transplantation four months earlier had failed, and a combined liver and kidney transplant operation was carried out

Aetiological grouping of the 26 patients together with age and sex of individual patients and their outcome

Diagnosis	No of cases	Age (in years) and sex	Outcome†
Biliary atresia	4	2 M; 11 M; 2 M; 7 F*	A 27 wk; A 21 wk; A 13 wk; A 10 wk
Inborn errors of metabolism:			
α_1 Antitrypsin deficiency	2	57 M; 14 F	D 3 wk; A 11 wk
Primary hyperoxaluria	1	18 M	A 8 wk
End stage chronic liver disease:			
Subacute hepatic necrosis	2	11 F*; 46 F*	A 25 and 3 wk; A 2 wk
Chronic active hepatitis	5	20 M; 36 F; 40 F; 17 F; 58 M	A 47 wk; D 7 wk; D 11 wk; A 15 wk; A 14 wk
Primary biliary cirrhosis	7	48 F; 38 F; 48 F; 46 M; 46 F; 50 F; 46 F	D 1 wk; D 3 wk; D 17 wk; D 3 wk; A 7 wk; D 4 wk; A 6 wk
Budd-Chiari syndrome	1	37 F	A 49 wk
Alcoholic cirrhosis	1	52 M	A 9 wk
Malignant liver disease:			
Primary hepatocellular carcinoma	2	10 F; 42 M	D 22 wk; D 1 wk
Secondary carcinoma	1	45 M	A 26 wk

*Given second transplant. †A=Alive. D=Died.

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with the aim of correcting the underlying metabolic defect in the liver and preventing further oxalate deposition in the tissues (R W E Watts *et al*, unpublished observations).

Primary biliary cirrhosis was the indication for operation in seven cases, and five patients had chronic active hepatitis, two of whom were in the younger age group. One patient from each group had liver failure from subacute hepatic necrosis (cases OL148 and 167) of four and six months' duration respectively and presumed to be due to non-A, non-B viral hepatitis. There were single cases of Budd-Chiari syndrome (case OL142) and alcoholic cirrhosis (case OL162). In each of these worsening liver function, diuretic resistant ascites, and intermittent encephalopathy with

and without variceal bleeding were prominent clinical features. Two of the three patients with malignant liver disease had primary hepatocellular carcinoma; in one, a 10 year old girl (case OL147), this arose in a non-cirrhotic liver, and in the other, a 42 year old man (case OL149), it occurred in association with persistent hepatitis B infection (serum anti-HBe positive). The third patient, a 45 year old man (case OL151), had metastatic deposits in both lobes of the liver from a previously resected colonic primary tumour. In each case detailed screening, including computed tomography, had been carried out to exclude tumour deposits outside the liver.

OPERATIVE TECHNIQUE AND IMMUNOSUPPRESSION

The donor and recipient operations and immediate postoperative management are detailed elsewhere.³ In all but one of the cases the biliary tract anastomosis was based on using the gall bladder as a conduit between the donor common bile duct and the recipient's bile duct or a Roux loop in the children with biliary atresia; in the remaining case (OL166) the donor gall bladder hung down from a long Riedel's lobe and an end to end common bile duct anastomosis was fashioned after removal of the gall bladder. Venous bypass was used in 10 patients in whom cross clamping of the inferior vena cava before removal of the diseased liver caused a pronounced fall in blood pressure. A venovenous circuit was used in the first six cases with catheters connecting the inferior vena cava and portal vein to the superior vena cava,² while in later cases the circuit was venoarterial with connecting catheters

FIG 1—Effect of retransplantation on liver function values in 7 year old girl (case OL161).

Conversion: SI to traditional units—Bilirubin: 1 $\mu\text{mol/l}$ $\approx$ 0.06 mg/100 ml.

placed between the inferior vena cava and the common iliac artery via saphenous vein and femoral artery cannulation respectively (R Y Calne *et al*, unpublished observations). A flow of 1.0–1.5 l/min was maintained with a magnetic drive centrifuge pump (Biomedicus; Thackery Ltd, Leeds) and systemic heparinisation avoided by using heparin bonded tubing with a low dose prostacyclin (epoprostenol) infusion into the proximal limb of the bypass circuit.

Immunosuppression was based on a combination of prednisolone and azathioprine (initially 1.0 and 1.5 mg/kg/day respectively). A course of Campath 1, a monoclonal antibody preparation,⁴ was given from days 3 to 12 postoperatively to all but five of the early patients in this series. Oral cyclosporin A 4 mg/kg/day was started as soon as the T tube was clamped, usually during the second postoperative week, the dose being subsequently adjusted so as to maintain whole blood concentrations of cyclosporin between 250 and 750 mg/l. Azathioprine was then stopped and, depending on progress, the dosage of prednisolone progressively reduced. Episodes of rejection were treated initially by intravenous methylprednisolone 10–15 mg/kg/day for three days.

Results

At review 16 of the 26 patients were alive, and in the younger age group only one death had occurred. Predicted actuarial survival for all patients was 48%, being 75% for the younger age group and 28% for the older patients. The one death in the younger age group was the 10 year old girl (case OL147) with a primary hepatocellular carcinoma. She had made a good recovery initially and was able to return home to Italy, but evidence of tumour recurrence was detected in the fourth postoperative month and she died shortly afterwards.

Of the nine patients in the older age group who died, five did so within four weeks of operation. In each instance heavy bleeding during the operation and in the early postoperative period appeared to have been the major adverse factor, three of the patients requiring re-exploration within the first 24–36 hours. Death occurred either as a direct result of the haemorrhage with persisting hypotension and rapidly developing ischaemic necrosis of the liver (case OL149) or, in three cases (OL145, 154, and 156), in the second to fourth postoperative weeks, as a result of combined respiratory, renal, and liver failure. One patient (case OL146) had required reoperation for bleeding after 24 hours and again six hours later. He then did well until day 18, when he had a massive unexplained colonic haemorrhage which proved fatal. The remaining four patients (cases OL144, 152, 155, and 165) died between one and six months after transplantation. All had recurrent infections, possibly aggravated by pre-existing malnutrition. In two cases (OL152 and 155) the primary site appeared to be an intrahepatic abscess, but by the time of death infection was generalised in all four, respiratory failure being the immediate cause of death. At different times *Staphylococcus aureus*, *Escherichia coli*, *Streptococcus faecalis*, and *Pseudomonas aeruginosa* were isolated from blood cultures, and terminally *Aspergillus fumigatus* was isolated in one case (OL156). All of these patients had periods of improvement when infection was controlled with antibiotics.

CURRENT SURVIVORS

Of the nine survivors in the younger age group, the four children with biliary atresia were doing particularly well 10–27 weeks after operation. Whereas before transplantation all had serum bilirubin concentrations exceeding 120 $\mu\text{mol/l}$ (7.0 mg/100 ml), at review three had concentrations within the normal range (3–20 $\mu\text{mol/l}$; 0.2–1.2 mg/100 ml). One, a 7 year old girl (case OL161) whose first transplant was from a 23 month old donor, required retransplantation. Postoperative recovery had been uneventful and she had already been extubated when on the fourth postoperative day she became rapidly unconscious. Bile output fell and became watery, her prothrombin time increased from five to 44 seconds prolonged, the serum bilirubin value doubled, and serum aspartate aminotransferase activity increased fivefold over 24 hours (fig 1). A suitable size donor organ was available (from a 12 year old) and retransplantation performed. At operation the initial liver graft was found to be enlarged, mottled, and darkish red and there was no pulsation in the hepatic artery proximal to the anastomosis. On opening the vessel blood clot was seen to extend back into the coeliac artery and the portal vein was also found to be full of clot. Thrombus was removed from both vessels with Fogarty catheters before creating the new anastomoses. The subsequent improvement in her clinical state and liver function values was remarkable (fig 1), and six weeks after receiving the second transplant she was discharged home well.

One child with biliary atresia and persisting jaundice (case OL150) had had recurrent cholangitis and shown some evidence of rejection but was improving. The 14 year old girl with α_1 antitrypsin deficiency (case OL160) was doing well, while the postoperative course of the 18 year old man with primary hyperoxaluria (case OL163) had been complicated by pancreatitis and acute tubular necrosis.

Of the three patients with chronic active hepatitis alive 14–47 weeks after transplantation, two were also in the younger age group. All three were much improved symptomatically with in each case an appreciable improvement in liver function values—return of prothrombin time from four seconds or more prolonged to normal, fall of over 40% in serum bilirubin concentration, and rise of over 25% in serum albumin concentration. Two of these patients required disobliteration of a thrombosed portal vein at the time of operation. In one, a 17 year old girl with chronic active hepatitis (case OL157), the preoperative ultrasound scan was in retrospect wrongly interpreted, with large collateral vessels being mistaken for a patent portal vein. Adherent and organised thrombus was removed by dissection, the softer clot within the lumen by a venous Fogarty catheter. Postoperative recovery was excellent and she was discharged home after three weeks with normal liver function values. The second patient was a 58 year old man with end stage cirrhosis of chronic active hepatitis (case OL158) in whom preoperative arteriography had shown a blocked portal vein and a large collateral circulation but who in all other respects was a suitable candidate. Recovery after transplantation was rapid, and at 14 weeks liver function values were normal. Follow up ultrasound examination and arteriography in the first case and repeat ultrasound examination in the second confirmed wide patency of the portal vein in both patients (fig 2).

Of particular note was the recovery of the 11 year old girl with progressive liver cell failure from subacute hepatic necrosis (case OL148), who at the time of transplantation had a prothrombin time maintained at 12 seconds prolonged only by virtue of a daily infusion of fresh frozen plasma. She was deeply jaundiced with ascites and intermittent encephalopathy. The operation went surprisingly well, with a blood loss of only 3 l, and there was a rapid clinical and biochemical improvement with return of the prothrombin time

to normal. Over the subsequent weeks she became deeply jaundiced again with a raised alkaline phosphatase activity, and liver biopsy at six months confirmed chronic rejection of the "vanishing bile duct" type.⁵ On 9 July 1984 retransplantation was performed and her early postoperative recovery was excellent, the serum bilirubin concentration having fallen from 536 $\mu\text{mol/l}$ (31.3 mg/100 ml) to 44 $\mu\text{mol/l}$ (2.6 mg/100 ml). The other patient, a 46 year old woman (case OL167) with subacute hepatic necrosis and a prolonged prothrombin time (14 s), also had a relatively uncomplicated operation (blood loss 5.5 l), although difficulty was experienced with the hepatic artery anastomosis because of the small size of the recipient artery. Postoperative recovery was uneventful until the second week, when hepatic artery thrombosis occurred and retransplantation was carried out. Her liver function had deteriorated severely, with a rise in prothrombin time from four to 63 seconds prolonged and an increase in serum aspartate aminotransferase activity from 203 to 3500 IU/l. Liver biopsy showed ischaemic necrosis. At operation on 29 July 1984 narrowing was found at the hepatic artery anastomosis with clot extending distal to this within the donor vessel. The new anastomosis was carried out using the recipient splenic artery.

FIG 2—Subtraction film from arteriogram in 17 year old girl (case OL157) showing patent portal vein three months after surgery in patient who required disobliteration at time of liver transplantation.

Two patients with primary biliary cirrhosis alive six and seven weeks after transplantation (cases OL164 and 166) were making steady progress. Both had serum bilirubin concentrations exceeding 500 $\mu\text{mol/l}$ (29.2 mg/100 ml) preoperatively, which fell by at least 70%. The two remaining adult surviving patients with end stage chronic liver disease were a 37 year old woman with Budd-Chiari syndrome (case OL142), who had normal liver function values 49 weeks after transplantation, and a 52 year old man with alcoholic cirrhosis, whose postoperative course was complicated by peritonitis after removal of the T tube. The one survivor of the three patients with carcinoma in the series, a 45 year old man with hepatic metastases (case OL151), was in his seventh month, although recurrence of tumour in the right pleura had recently been detected.

Discussion

A most encouraging feature to emerge from this series was the excellent results in the younger age group. This has also been reported by Starzl *et al*, who in published figures for 1982 showed a survival of 57% (16 out of 28 cases) for patients less than 18 years old and 44% (15 out of 34) for older patients.² Thus in considering overall results for any series the proportion of patients in different age groups should be taken into account. Although until recently we were reluctant to consider young patients for transplantation because of the side effects of long term corticosteroid treatment, cyclosporin A now permits the dosage of prednisolone to be reduced

and in some cases discontinued. Thus of 11 patients in the present series surviving more than three months, two were receiving cyclosporin A alone and in the nine others prednisolone had already been reduced to between 5 and 15 mg/day. Also until recently we were restricted by the shortage of donor organs for this age group. The recent nationwide publicity in Britain on behalf of Ben Hardwick, however, a 2 year old boy with biliary atresia (case OL150), has resulted in many more donor organs being made available for liver grafting.

The greater availability of donor organs also means that greater use can be made of retransplantation. This allows errors of surgical technique to be corrected and livers that show signs of chronic rejection or infection to be replaced. Retransplantation was a prominent feature of the approach of Starzl *et al*, with a 30% retransplant rate in their series.² Our rate of 11.5% (three of 26 patients) was still low by comparison, and greater use earlier in the series would almost certainly have resulted in more of the patients surviving.

Failures in our older age group of patients appeared to fall into two main groups, those attributable to heavy perioperative bleeding and those due to recurrent infection. Krom and colleagues have similarly reported a substantial difference in median blood loss between non-survivors and survivors (25 000 ml and 7500 ml respectively), although as in our series they too had patients who bled heavily but survived.⁶ Venous bypass as introduced by Starzl *et al* (and which they use in almost all of their adult patients²) was employed in 10 patients in our series. Bypass decompresses the inferior vena cava and portal vein and prevents the accumulation of potassium and acid waste products while also helping to maintain blood pressure and perfusion, particularly of end organs such as the kidney. The latter is almost certainly a factor in better postoperative function and less predisposition to cyclosporin A toxicity. Of particular note were the excellent results obtained in the two patients with an occluded portal vein, which hitherto had been regarded by us as a contraindication to liver transplantation. In both cases venous bypass was used.

Infection during the early postoperative period should become less of a problem if, as a result of using cyclosporin A, the dose of prednisolone used in this period can be rapidly reduced. Our early experience with intravenous cyclosporin A started within 12 hours of transplantation was not encouraging, with the occurrence of frequent, severe pulmonary and renal complications.⁷ This toxicity may, however, have been a result of inadequate control of blood concentrations of cyclosporin A, and Starzl *et al* continue to base immunosuppression on intravenous cyclosporin A given soon after operation and continued for four to six weeks until adequate absorption of the drug given by mouth can be shown.⁸ Poor nutritional state preoperatively may be another factor which increases a patient's liability to infection, although probably most patients with end stage chronic liver disease, whether children or adults, will be undernourished.

Even though overall survival results in the older age groups were not as good as in the children, the appreciable symptomatic as well as biochemical improvement in the patients who did survive was remarkable. This applied not only to primary biliary cirrhosis but also to other types of end stage chronic liver disease such as chronic active hepatitis. Of 20 patients in our total series treated for this condition, the actual one year survival was 40%. Patients with Budd-Chiari syndrome seem to do particularly well after liver transplantation; thus of eight patients with Budd-Chiari syndrome given transplants to date, five were alive at one year and four were alive one to seven and a half years after operation. The recurrence of tumour in two of the three patients in this series with malignant liver disease despite the most careful preoperative screening for extra-hepatic deposits again highlights how difficult screening is. Nevertheless, some patients with malignancy are cured by liver transplantation, and this includes our longest survivor, now in his ninth year after operation (case OL43).⁹

The ability to carry out transplantation in the two patients with subacute hepatic necrosis merits special comment. In our experience mortality in this group with a presumed non-A, non-B aetiology (and no autoimmune markers) is 80-90%.¹⁰ The difficulties of trans-

plantation in this group and in fulminant hepatic failure are considered elsewhere.¹¹ Our current experience gives considerable hope for a greater use of liver grafting in these very severe types of liver failure. Transplantation for inborn errors of metabolism is also likely to increase. We have given transplants to patients with α_1 antitrypsin deficiency, galactosaemia, and one with Wilson's disease (case OL119), who was alive with normal copper metabolism two years after transplantation,¹² and in the present series two further cases of α_1 antitrypsin deficiency and one of primary hyperoxaluria (R W E Watts *et al*, unpublished observations) were treated in this way. Starzl *et al* are also performing liver transplant operations in a wide range of metabolic disorders, including recently a 6 year old with familial hypercholesterolaemia, in the hope that the grafting of a normal liver, as in our patient with hyperoxaluria, will correct the underlying metabolic disturbance.¹³

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Outside Europe

Drugs and the Third World

TESSA RICHARDS

Drugs in the Third World are handled in much the same way as other commodities. Traders who today deal in drugs (tomorrow it might be bananas) expect to make a good living, as do the wholesalers and retailers, and business practices may be less than scrupulous. Bureaucracy is unwieldy, conditions of storage poor. Drugs and vaccines sit in stores and custom houses in fridges that do not work, gently deteriorating until finally they reach an outlet. This outlet may be an untrained "compounder" of medicines who lacks the knowledge or skills to handle drugs appropriately. Drug pilferage and substitution is common and neither dealers nor patients may get what is promised on the glossy outside of a Western package. Drugs are in short supply, as are suitable packets and containers. Sterile preparations are dispensed in unsterile containers; many patients bring their own. Compliance with drug treatment is universally poor. These were just some of the problems that were outlined at a recent symposium (5 December) in London organised by the Association of Medical Advisors in the Pharmaceutical Industry.

The meeting was entitled The Pharmaceutical Industry and Third World Medicine—a global enough topic and, as the chairman Sir Kenneth Stuart from the Wellcome Trust pointed out, one which is underpinned by vast problems; compounded by the fact that there is no appropriate mechanism for cooperation between the Western based pharmaceutical industry and the developing countries. In his opening comments Sir Kenneth hoped that the meeting, which was attended by about 50 medical advisers to the pharmaceutical companies, would generate practical policies to

bridge the gap between the industry and the Third World. Few could doubt that the industry needs to adopt a new approach but it was perhaps overambitious to expect more of this meeting than a thorough airing of the problems and a sprinkling of good ideas—and in this respect expectations were amply fulfilled.

Professor P Thairu from the Commonwealth Secretariat dispensed with lip service to the Third World and presented a clear picture of near comprehensive chaos, which he said surrounds all aspects of the supply, distribution, storage, quality control, promotion, and dispensing of drugs. To make matters worse, developing countries are unable to forecast their pharmaceutical needs for, among other reasons, illness is unrecognised, misdiagnosed, and unrecorded. Traditional healers have not been slow to lace their remedies with Western medicines, said Dr J N Banerjee, who is chairman of the Commonwealth Pharmaceutical Association. This is particularly worrying since few of these healers have more than a passing acquaintance with pharmacology, and are ignorant of indications for treatment, dose schedules, and side effects. Thus mixtures of steroids, antibiotics, and hormones are dished out with little care in busy local markets, which serve the 70-80% of the total population which lives in rural communities. These people have access to only 20% of the country's drugs (the rest go to people living in the urban areas) and avidly spend money on medicines. Traditional healers promote and advertise their cures freely and, whether they get paid in cash or with two chickens, most are wealthy.

Long turning circles

From such a catalogue of problems clearly the Third World's pharmaceutical needs can never be solved by simply supplying the countries concerned with sufficient of the appropriate drugs. For, even if they were able to define "sufficient" and "appropriate" and were prepared to spend their limited supplies of foreign exchange on