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Reprinted from

THE BIOLOGY AND SURGERY OF TISSUE TRANSPLANTATION

edited by

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Blackwell Scientific Publications
Oxford and Edinburgh
1970

20 · Clinical aspects of orthotopic liver transplantation*

Since the first orthotopic transplantation of the human liver was performed in Denver in 1963, 25 patients have had 26 such operations [19-29]. However, during the past 21 months, better understanding of histocompatibility matching, the addition of ALG to the immunosuppressive regimen, and the use of more adequately preserved homografts has made it possible to achieve more encouraging although still unsatisfactory results.

Recipients

The patients ranged in age from 12 months to 68 years. Thirteen were male and 12 female. The indication for transplantation was congenital biliary atresia in 13 cases, hepatoma with or without cirrhosis in 11, and alcoholic cirrhosis in one. One patient with biliary atresia received a second liver transplant 66 days following the initial operation, because of severe rejection of the homograft; he is still alive 7½ months after the second operation.

Donors

Careful selection of donors was necessary. Any potential donor who had suffered from prolonged periods of hypotension and poor tissue perfusion was found to be unsuitable. If the liver from such a donor was used severe and persistent bleeding occurred and, in addition, more delayed effects of acute hepatic failure usually led to the death of the recipient.

There were 21 male and 6 female donors, ranging in age from one to 73 years. The majority died of acute head injuries or of non-traumatic

* The research reported in this paper was supported by United States Public Health Service Grants AM-06344, HE-07735, AM-07772, AI-04152, FR-00051, FR-00069, AM-12148, and AI-AM-08898.

neurologic disorders. Prior to the death of the donor ABO grouping was determined. In later cases, histocompatibility matching, using the Terasaki technique, was utilized to select the best possible recipient from our waiting-list.

With many of the adult donors the femoral vessels were cannulated, as soon as possible after death was pronounced, and partial cardio-pulmonary bypass was instituted [14, 15, 19]. This provided satisfactory perfusion of the liver with oxygenated, cooled blood. Donor hepatectomy was then performed. For pediatric donors, cardio-pulmonary bypass was usually not used but the superior mesenteric vein was rapidly cannulated and the liver was perfused with a cold electrolyte solution at a temperature of 2-4° C [19, 29]. Egress for the perfusate was provided by making an opening in the inferior vena cava.

On many occasions there was a considerable time interval between removal of the donor liver and completion of the recipient hepatectomy. Most often this delay was caused by a difficult recipient operation resulting from numerous adhesions and/or collateral channels. In these cases the liver was not immediately transplanted but was protected from ischaemia by perfusing it with diluted blood in a hyperbaric oxygen chamber, where it was exposed to oxygen at a pressure of 40 pounds per square inch, and maintained at a temperature of 4° C [5]. Thirteen livers were preserved under these conditions for periods ranging from 61 minutes to 240 minutes [29]. With one exception all these livers functioned satisfactorily following revascularization in the recipient. The longest period of total hepatic ischaemia, from the death of the donor to revascularization in the recipient, was 7½ hours. This liver functioned well and the recipient is still alive more than 11 months after operation.

The recipient operation

Removal of the recipient liver involved severance of the structures entering and leaving the liver. The suprahepatic vena cava of the donor liver was anastomosed to the recipient vena cava, followed by the infrahepatic vena caval anastomosis. The portal venous and hepatic arterial reconstructions were then performed. Shunts to temporarily decompress the portal vein and vena cava during the performance of these anastomoses [18] have been found not to be necessary [29].

Following completion of the vascular anastomoses and restoration of blood-flow a cholecystoduodenostomy was the procedure of choice to

provide biliary drainage [23], except in the occasional case where the donor cystic duct ran parallel to the common bile duct and entered it very low down. There was a danger of accidentally ligating such a duct together with the common bile duct and thus obtaining no biliary drainage. Where this anatomic variation was recognized we removed the donor gall bladder and performed a choledocho-choledochostomy [29].

A splenectomy was usually performed not only for reasons of immunosuppression but also because pre-existing hypersplenism was common in these cases.

Immunosuppression

In the early cases immunosuppression was with Azothioprine and Prednisone only. However, it was found that there was practically no safety margin between effective and lethal doses of Azothioprine [21]. Subsequent experience bore out the fact that Azothioprine had to be given to human liver recipients in incongruously small doses [29]. Several factors were probably responsible. First, pre-existing liver disease may have depleted the patient's haemo- and lymphopoietic reserves. Second, the liver plays an important role in the detoxification of Azothioprine, and ischaemic or immunologic injury to the liver may have reduced its capacity to metabolize Azothioprine. In the presence of impaired liver function it was necessary to reduce the dosage of Azothioprine to prevent the complication of bone marrow depression.

In the last 21 months we used triple drug therapy for immunosuppression—the two drugs mentioned above plus antilymphocyte globulin [22-25, 27-29]. The addition of the latter agent has considerably improved our results of kidney transplantation [23, 26] and we believe that it is one of the agents responsible for long-term survival in liver transplantation.

Initially ALG was used only for the first 4 months following liver transplantation. However, several patients showed the first evidence of rejection only when ALG therapy was discontinued and in our later cases ALG therapy has been prolonged for periods of up to 8 months [29].

Intra- and postoperative problems

Physiologic considerations

Apart from technical considerations the main problems encountered were concerned with maintenance of an adequate blood volume,

correction of acid-base abnormalities, and prevention of hypoglycaemia. The operation was often rather bloody because of pre-existing portal hypertension and because of the need to divide numerous vascular adhesions and collateral channels. Blood replacement kept pace with loss and fresh blood was preferred to avoid the hyperkaliaemia and acidosis which frequently complicate transfusions of stored blood.

Metabolic acidosis was frequent during the anhepatic phase [1, 27] and was compounded by the administration of large quantities of ACD blood. Repeated estimations of arterial blood gases, pH and bicarbonate levels were necessary and abnormalities were corrected by the administration of appropriate amounts of sodium bicarbonate.

A fall in the blood sugar level had to be prevented during the anhepatic phase and during the early post-transplantation period. This complication occurred in the first postoperative hours in spite of the fact that other measures of hepatic function appeared to be adequate [1]. Hypoglycaemia was avoided by administering dextrose intravenously at the rate of 0·1-0·5 gm/kg per hour during surgery and afterwards. The blood glucose level was monitored at frequent intervals.

Large quantities of ACD blood may produce direct myocardial depression even with perfect acid-base control. This effect was counteracted by the intermittent administration of 300 to 400 mgm of calcium gluconate or chloride intravenously [17, 32]. During the first few hours postoperatively the endotracheal tube was not removed. Ventilatory support was not discontinued until the patient began objecting to the presence of the endotracheal tube. Meticulous and frequent tracheobronchial toilet was essential to prevent atelectasis and pneumonia.

The serum electrolytes were monitored frequently as hypokaliaemia was frequent soon after transplantation, partly because of the removal of potassium from the circulation by the transplanted liver and partly because of the administration of large quantities of sodium bicarbonate to correct acidosis [12, 30].

Coagulation problems

Haemorrhage. Intraoperative bleeding was copious in some cases. It was found necessary to quickly examine the entire operative field for major bleeding sites, particularly at the anastomoses. If no localized bleeding site was responsible then the cause was found to be a deficient clotting mechanism, the severity of which was roughly proportional to the magnitude of ischaemic injury to the liver. This resulted in intravascular coagulation associated with pathologic fibrinolysis [3, 4, 10, 11,

16] coupled with temporary cessation of the synthesis of proteins essential for coagulation [31]. Exhaustive efforts were made to secure mechanical haemostasis of capillary bleeders with suture ligatures and cautery. If bleeding persisted, the prevention of fatal haemorrhage required the use of thrombogenic agents such as EACA, fibrinogen, and protamine sulphate. With better quality homografts, thrombogenic agents were unnecessary. Further, they could have potentiated the already significant risk of delayed intravascular thrombosis.

Clotting. Thrombosis of the main hepatic artery occurred in one of our patients and in a patient treated by Birtch [2] of Boston. Both recipients died. In these 2 cases, superb liver grafts had been provided. The 'auto-anticoagulation' effect which follows hepatic ischaemia was probably thereby lost. Under optimal clinical circumstances of organ procurement and preservation, it may therefore be advisable to institute prophylactic anticoagulation after liver transplantation.

A homograft with 2 hepatic arteries underwent partial gangrene within 48 hours of transplantation, when the anastomosis of the smaller right branch thrombosed. Resection of the necrotic liver was followed by survival for 4½ months.

Non-conventional arterial anastomoses were necessary in 2 patients with gross congenital vascular anomalies. Both arteries became pinched or kinked postoperatively but did not thrombose. However, both patients died in the early postoperative period of arterial insufficiency [29].

Another patient died of portal vein thrombosis.

Other complications

Air embolism via tears which occurred in the inferior vena cava or its tributaries during recipient hepatectomy occurred in several cases but was symptomatic in only one patient [29].

Paralysis of the right diaphragm occurred in 4 patients as a result of including a portion of the diaphragm in the vascular clamp used to occlude the suprahepatic vena cava. In most cases this complication could be avoided by developing a longer vena caval cuff in the recipient and by taking care not to include any diaphragm in the bite of the vascular clamp.

Gastro-intestinal ulceration or bleeding occurred in the early post-operative period in patients who received poor-quality liver grafts. Later in the postoperative period gastro-intestinal bleeding occasionally occurred as a complication of high dosage steroid therapy. This usually

responded to conservative management and no patient required surgical treatment for the control of haemorrhage.

Pulmonary embolism was encountered in 3 patients treated early in our experience [19, 20]. Possible causes of this complication were the use of venous bypass shunts and the administration of clot-promoting agents. After these practices were discontinued, there were no additional examples in the next 22 recipients.

Arterial hypertension developed postoperatively in 3 patients. Abnormally high serum levels of norepinephrine and/or tyramine were found in 2 of the patients [29]. Probably tyramine degradation by the liver was depressed in at least some of the recipients. This agent is believed to exert a vasoconstrictor effect by causing release of norepinephrine from adrenergic nerve endings.

Varieties of rejection

Acute

Rejection occurred in 1 of 3 forms—a mild subclinical type, an acute explosive variety, and an indolent, slowly progressive form [29]. The first 2 varieties were reversible with appropriate therapy, but the latter kind showed little tendency to regress. This latter variety presented with hepatomegaly and a picture resembling a slowly developing obstructive jaundice. The clinical picture in the two former types varied in degree and presented with several of the following features: anorexia, extreme fatiguability, back pain, hepatomegaly, light-coloured stools, dark urine, fever, leucocytosis, fluid retention with gain in weight, hyperbilirubinaemia, and elevation of the serum transaminase and alkaline phosphatase levels. In severe cases depression of the serum protein levels and of the liver-based clotting factors occurred. Serial scanning of the liver using 99 M-technetium was very helpful in making the diagnosis of rejection [9, 29]. In mild cases the scan showed enlargement of the liver. In more severe cases there was poor take-up of the isotope by the liver, or there was paradoxical decrease in size of the liver despite clinical evidence of hepatomegaly.

Investigations in dogs [13] and pigs [7] have shown that hepatic rejection often underwent spontaneous resolution without any change in therapy or in some animals in the absence of any therapy at all. This experience initially caused us to adopt a policy towards hepatic rejection different from that which is standard practice in our institution after renal transplantation. When renal homografts undergo deterioration,

steroid doses are invariably increased and maintained at whatever levels are necessary to restore good kidney function. With rejection in liver homografts we have often maintained steroid dosage at pre-existing levels or have even decreased the quantities. In several cases, episodes of acute rejection have reversed under these conditions. However, it is our present view that therapy should be intensified at these times. We now believe that adherence to a less aggressive therapeutic policy was probably the most important single etiologic factor in the septic hepatic infarctions to be mentioned below.

Chronic

It was mentioned earlier that the discontinuance of ALG treatment in the majority of patients was followed shortly afterwards by signs of delayed rejection. The pace of events with rejection occurring months after operation was relatively slow. The principal metabolic abnormalities detected were those of progressive obstructive jaundice [29]. The process was exceedingly difficult or impossible to reverse despite significant adjustments in immunosuppressive treatment.

The consequences of late rejection were ordinarily well tolerated since the functions of hepatic synthesis remained essentially intact. The two presently living patients in our series who have had the longest follow-ups have been jaundiced for 8 and 10 months respectively. The total postoperative interval of observation in both instances now exceeds 1 year.

Septic hepatic infarction

A special complication of rejection was the development of regional hepatic gangrene, which occurred in 5 consecutive cases early in our series [24, 25, 29]. This calamity probably resulted from a combination of factors—(a) acute rejection, with its concomitant decrease in blood flow through the liver, (b) lack of support of the transplanted organ, which caused rotation of the organ backwards and medially, with resultant kinking and thrombosis of the right hepatic artery, and (c) invasion of the infarcted area by intestinal micro-organisms [6]. The resulting septic infarct produced a triad of gram-negative septicaemia, markedly elevated serum transaminase levels, and the development on serial liver scans of large areas of persistently absent isotope concentration in the homograft. Treatment required early and extensive debridement of dead liver tissue, drainage of the affected portion of liver and administration of the appropriate antibiotics. Despite these measures

4 of the 5 patients died soon after the development of this complication. We believe that the best treatment is prophylaxis.

Prevention of this complication requires intensive immunosuppressive therapy, especially during the early postoperative period to avoid rejection; fixation of the falciform and other ligaments of the homograft to the companion structures in the recipient to avoid distortion of the right hepatic artery, and administration of antibiotics for 1 or more weeks after the operation. Since these measures have been adopted we have not had any further cases of septic hepatic infarction.

Infectious complications

Increased susceptibility to infection is a problem common to the transplantation of all organs as a result of lowering the reactivity of the host by the use of immunosuppressive drugs. The risk of infection was found to be disproportionately great after liver transplantation [8, 29], possibly because of a loss of the normal reticulo-endothelial function of bacterial filtration. In consequence, there may be greater permeability of the transplant to gastro-intestinal flora carried to it through the portal venous and biliary duct systems. It is also possible that depression of the reticulo-endothelial activity of the graft may undermine the total host defences against infection of other organ systems. Because of the environment in which the orthotopic transplant must exist it is obvious that antibiotic therapy against gram negative organisms is often required.

Even in the case of well-functioning grafts episodes of bacteraemia were common while patients with poorly functioning transplants were particularly prone to infections especially septicaemia with gram negative organisms. Large doses of immunosuppressive drugs and prolonged use of antibiotic agents further increased the patient's susceptibility to infection. Important features of the infections encountered were a predisposition to pneumonitis; a tendency for localized sepsis to become multifocal; and the frequent etiologic role of gram-negative bacteria, fungi, and other less common micro-organisms of normally low pathogenicity.

Tumour recurrence

In 3 of 4 patients, operated upon for hepatoma, metastases of the tumour made their appearance within 3 to 5 months of the transplant operation [29]. These were particularly prominent in the lungs, where massive

metastases ultimately developed. It is possible that microscopic pulmonary metastases were present at the time of the transplant operation, and that the decreased host resistance induced by the immunosuppressive drugs permitted the tumour cells to flourish. In 3 of the patients the transplanted liver itself became the seat of metastatic deposits.

Survival

Of the 25 patients 14 lived for periods less than 8 weeks. Death in this early period resulted from several causes—the use of an organ damaged by ischaemia; technical problems which resulted in occlusion of the arterial or venous inflow of the liver; the use of large doses of immunosuppressive agents which resulted in overwhelming infection; and fatal pulmonary embolism.

Eleven patients survived for periods of 8 weeks or longer. Seven of these patients survived more than 6 months and 3 survived more than 1 year [29]. At present 7 patients are alive 13, 12, 11, 10, 8, 6 and 1 month post transplant respectively. Of these patients 2 have reached the terminal stages of metastatic hepatoma; 3 have chronic rejection but are otherwise in satisfactory general condition; and 1 has intra-abdominal complications following his transplant operation 1 month ago. Only 1 patient, a 4 year-old-boy, who had a transplant performed 8 months ago for biliary atresia, is in perfect health.

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