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Liver transplantation in the management of bleeding oesophageal varices

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The vast majority of patients who require liver transplants have significant portal venous hypertension, and their liver replacement is specifically aimed to treat three major complications of portal hypertension, namely, bleeding oesophageal varices, refractory ascites and encephalopathy (liver failure).

Variceal haemorrhage and ascites can be treated effectively by various types of portal decompression surgery, but these procedures invariably decrease hepatic blood flow and hence worsen the function of an already compromised liver. The enthusiasm for treating oesophageal varices and ascites with non-selective portosystemic shunting started to wane more than two decades ago when it became apparent that the price of preventing haemorrhage from oesophageal varices and intractable ascites in this manner was dehumanizing encephalopathy and progressive hepatic dysfunction (Jackson et al, 1971; Resnick et al, 1974).

With the development of potent and specific diuretic drugs, truly intractable ascites is extremely uncommon. When it does occur, more appropriate therapy than portosystemic shunt will often be a peritoneojugular shunt. Chronic hepatic encephalopathy can rarely be managed by medical means, and it is effectively treated only with liver transplantation. Thus, the principal problem in portal hypertension for which therapeutic planning must be done is the haemorrhage from oesophageal varices.

Prophylactic and therapeutic uses of anti-β-adrenergic agents and endoscopic sclerotherapy play a significant role in the management of oesophageal varices. Various types of portosystemic venous shunting have been evaluated as to their efficacy in preventing both haemorrhage from varices and accelerated decline of hepatic function.

In our centre, where there is a chronic shortage of organs, Child's A patients who have had variceal bleeding are systemically screened for selective splenorenal shunts, performed electively. The procedure is being used on a trial basis because it is attended by a lower incidence of encephalopathy than is seen after non-selective shunts. Forty patients have been entered with no perioperative deaths but longer follow-up will be necessary to assess the validity of this approach. Five of the 40 have come to successful transplantation during the first 12 months after their Warren

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shunts, which caused no technical difficulties at the time of grafting. In most cases, the shunt is removed by splenectomy.

Liver transplantation has emerged as a safe and preferred treatment of many patients with end-stage liver diseases, the vast majority of which resulted in portal hypertension (Starzl et al, 1982). Whether the graft is placed in the natural location (orthotopic) or ectopic site (heterotopic or auxiliary), liver transplantation invariably corrects the portal hypertension and treats most effectively bleeding varices, intractable ascites and encephalopathy.

Except in isolated cases or small series, auxiliary transplantation has not provided satisfactory results. Consequently, we will concentrate in this chapter on the role of orthotopic liver transplantation in the management of portal hypertension, particularly of bleeding oesophageal varices. Also, we will examine the relationship of transplantation to other therapeutic modalities.

INCIDENCE OF PORTAL HYPERTENSION, BLEEDING OESOPHAGEAL VARICES AND PORTAL VEIN THROMBOSIS AMONG LIVER TRANSPLANT RECIPIENTS

The liver diseases of the first 1000 patients who received liver transplants under cyclosporin-steroid therapy (March 1980 to July 1987) are listed in Table 1 with the incidences of bleeding from oesophageal varices.

More than 90% of the patients had end-stage chronic liver disease with significant portal hypertension. Furthermore, 22 patients had undergone non-selective shunt, 15 patients had undergone selective shunt, and five

Table 1. Liver diseases of 1000 patients who received liver transplants between March 1980 and July 1987 and the incidences of bleeding from oesophageal varices.

Diseases	No. of patients	No. of oesophageal bleeders
Cirrhosis	319	115 (36%)
(postnecrotic, cryptogenic, alcoholic)	(41)	(15) (37%)
Biliary atresia	180	38 (21%)
Primary biliary cirrhosis	166	63 (38%)
Liver-based inborn metabolic errors (α_1-antitrypsin deficiency, Wilson's disease, etc.)	98	35 (36%)
Primary sclerosing cholangitis	82	32 (39%)
(with bile duct cancer)	(8)	
Hepatobiliary malignancy	45	0
Fulminant hepatic failure	37	0
Secondary biliary cirrhosis	21	8 (38%)
Budd–Chiari syndrome	15	2 (13%)
Familial cholestatic syndrome	15	4 (27%)
Congenital hepatic fibrosis	6	5 (83%)
Others	16	0
Total	1000	302 (30%)

With these technical improvements, all types of portal hypertension (prehepatic, intrahepatic and posthepatic) or any combination of them can be effectively treated by orthotopic liver transplantation. This has widened the indications for treatment.

RESULTS OF LIVER TRANSPLANTATION FOR PATIENTS WITH END-STAGE LIVER DISEASE AND BLEEDING FROM OESOPHAGEAL VARICES

The overall survival rates of the first 1000 consecutive patients after liver transplantation with cyclosporin-steroid therapy (March 1980 to July 1987) were 74% at 1 year, 71% at 2 years, 67% at 3 years, 65% at 4 years, and 64% at 5 years, when they were calculated by the method of Kaplan–Meier as of September 1987 (Iwatsuki et al, 1988a). The overall survival rates under cyclosporin-steroid therapy were unchanged when they were re-examined in the consecutive 1469 recipients as of July 1989 (Starzl and Demetris, 1990) and in the consecutive 1583 recipients as of July 1990 (Gordon et al, 1991). However, the survival rates appeared to be improved starting in August 1989 when a novel immunosuppressive drug, FK-506, was introduced to our clinical trial (Starzl et al, 1989; Todo et al, 1990, 1991; Fung et al, 1991). The 1-year survival rate of 409 liver recipients treated with FK-506 has risen to 85% as of July 1991.

The survival rates of 302 variceal bleeders among the first 1000 consecutive liver recipients under cyclosporin-steroid therapy were 79% at 1 year, 74% at 2 years, and 71% at 3, 4 and 5 years as of February 1988 (Iwatsuki et al, 1988b). There was no statistically significant difference in the survival rates among the patients with the five most common liver diseases shown in Table 1.

The survival rates of the first consecutive 1000 liver recipients under cyclosporin-steroid therapy were updated as of September 1991, with a minimum follow-up of 4 years. One- to 5-year survival rates of the 1000 patients were 73%, 69%, 67%, 65% and 64%, respectively. Those of the 302 variceal bleeders were 80%, 77%, 75%, 74% and 71%, respectively. Thus, the actuarial survival rates calculated in 1987 and 1988 precisely predicted the actual survival rates in 1991.

LIVER TRANSPLANTATION FOR ALCOHOLIC CIRRHOSIS

Alcoholic liver disease is the most common form of liver disease in the USA and other Western countries. However, the use of liver transplantation to treat patients with end-stage alcoholic cirrhosis has long been debated. We have been treating some of the patients with end-stage alcoholic liver disease by orthotopic liver transplantation. During the pre-cyclosporin era between 1963 and 1979, 15 patients (18% of adult recipients) with alcoholic cirrhosis were transplanted. The first eight alcoholic recipients died peroperatively. However, four of the next seven patients survived more than 4 years. Three of the four patients are still alive and in good health after 17, 15 and 14 years,

respectively. None has returned to drinking. During the cyclosporin era between 1980 and 1989, 134 alcoholic patients (12% of adult recipients) received liver transplants. One- to 4-year survival rates were 81%, 75%, 73% and 73%, respectively, as of July 1990 (Gordon et al, 1991). These survival rates were better than those of patients with viral hepatitis B and those with hepatic malignancy. Moreover, nearly 90% of the transplant survivors remained alcohol abstinent.

Although abstinence was considered to be a favourable factor, a 'dry' period of specific duration was not required before transplantation since this would invite systematic falsification of the medical history and because death would often be the price of a significant wait. Instead, acknowledgement of the alcoholism problem is expected and commitments not to drink in the future are obtained from the patient and family. Going through a trauma of such magnitude as liver transplantation seemingly has been the starting point for long and permanent abstinence and usually for rehabilitation. For the last several years, however, extensive psychiatric and social support has been systematically provided, as the number of alcoholic liver transplant candidates has been increasing. The fact that relapses into alcoholism have been uncommon after liver transplantation weakens the potential objection that provision of a new liver is a futile gesture as well as a waste of an organ.

ROLE OF LIVER TRANSPLANTATION IN THE MANAGEMENT OF BLEEDING OESOPHAGEAL VARICES

The survival rates after liver transplantation for patients with advanced liver disease (Child's class C) who had had bleeding from oesophageal varices are quite satisfactory as presented earlier, and there is little doubt of the value of liver transplantation in this situation. Nevertheless, the results achieved by liver transplantation were compared with those reported in nine well-studied control trials of therapeutic shunt operations (Table 2). All of these well-designed studies failed to show the survival superiority of non-selective shunt over medical management (Jackson et al, 1971; Resnick et al, 1974; Reynolds et al, 1981), that of selective shunt over non-selective shunt (Conn et al, 1981; Langer et al, 1985; Millikan et al, 1985), or that of selective shunt over chronic endoscopic sclerotherapy (Warren et al, 1986; Rikkers et al, 1987; Teres et al, 1987).

As the outcomes of shunt operations, sclerotherapy or medical management are highly influenced by the hepatic functional reserve of the patients, the results of one study cannot be simply compared with those of another. More than 75% of the patients in each report listed in Table 2 had good hepatic function or moderately impaired hepatic function (Child's class A and B), and fewer than 25% of them had advanced hepatic dysfunction (Child's class C). On the other hand, all the patients who received liver transplants had advanced or far-advanced hepatic dysfunction; many of them had been rejected for shunt operation and some of them had already had a shunt operation. Despite this severe disadvantage in preoperative condition, the survival rates of liver transplant recipients who had had

variceal bleeding were better than or similar to those of patients who had other kinds of conventional therapy (Table 2).

Because surgical therapy for oesophageal varices is usually withheld from the patients with advanced hepatic dysfunction (Child's class C), the literature contains few survival data for these patients. In Table 3 the results obtained by liver transplantation are compared with those achieved in patients with advanced hepatic dysfunction after conventional surgical therapy (Turcotte and Lambert, 1973; Yamamoto et al, 1976; Warren et al, 1982; Rikkers et al, 1984; Chandler et al, 1985; Spence and Johnston, 1985;

Table 2. Survival comparison among various treatments for bleeding oesophageal varices (Child's classes A, B, and C).

Treatment	No. of patients	Survival rates (%)				
		1 yr	2 yr	3 yr	4 yr	5 yr
Jackson et al (1971)						
Non-selective shunt	67	80*	73*	62*	58*	55*
Medical	77	80	66	43*	35*	32*
Resnick et al (1974)						
Non-selective shunt	54	70*	58*	50*	48*	48*
Medical	25	67*	52*	40*	40*	40*
Reynolds et al (1981)						
Non-selective shunt	41	—	72*	64*	52*	44
Medical	37	—	60*	44*	36*	22
Conn et al (1981)						
Selective shunt	24	76*	70*	—	—	—
Non-selective shunt	29	70*	67*	—	—	—
Langer et al (1985)						
Selective shunt	38	80*	76*	63*	54*	51*
Non-selective shunt	40	90*	85*	70*	56*	56*
Millikan et al (1985)						
Selective shunt	26	85*	77*	65*	60*	55*
Non-selective shunt	29	80*	72*	70*	65*	60*
Warren et al (1986)						
Sclerotherapy†	36	90*	84	82*	82*	—
Selective shunt	35	70*	59	45*	45*	—
Rikkers et al (1987)						
Sclerotherapy	30	77*	61	60*	50*	—
Selective shunt‡	27	75*	65	60*	39*	—
Teres et al (1987)						
Selective shunt	57	90*	90*	82*	70*	70*
Sclerotherapy	55	81*	75*	65*	65*	65*
Iwatsuki et al (1988b)						
Liver transplantation	302	79	74	71	71	71
Iwatsuki et al						
Liver transplantation (update 1991)	302	80	77	75	74	71

* Value estimated from survival curve.
† Sclerotherapy failures were rescued by surgical therapy.
‡ Twenty-three selective shunts and four non-selective shunts.

Iwatsuki et al, 1988b). It is obvious that the survival rates of liver transplant recipients are far better than those achieved by conventional types of surgical therapy when the liver disease is advanced.

Should all the cirrhotic patients be treated with liver transplantation when they have significant episodes of variceal haemorrhage? The answer is obviously no, because chronic endoscopic sclerotherapy is quite effective in controlling the haemorrhage from oesophageal varices, and the survival rates after sclerotherapy are superior or equal to those of shunt operations providing the sclerotherapy failures are rescued by surgical intervention (Warren et al, 1986; Rikkers et al, 1987; Teres et al, 1987).

The role of endoscopic sclerotherapy in the treatment of bleeding oesophageal varices has been well established. However, the sclerotherapy cannot be effectively applied to gastric varices, and has its own special complications, such as oesophageal perforation or stricture of the distal oesophagus. The incidence of these complications rises astronomically when sclerotherapy is used during a crisis such as exists during active bleeding and especially if hepatic failure is a co-factor.

Portosystemic shunt operations should be limited to those who have failed endoscopic sclerotherapy but who still have excellent hepatic function. Although the survival rates after transplantation are not jeopardized by previous portosystemic shunt operations, the actual liver transplant

Table 3. Survival comparison among various treatments for bleeding oesophageal varices (Child's class C, poor liver function).

Treatment	No. of patients	Survival rates (%)				
		1 yr	2 yr	3 yr	4 yr	5 yr
Turcotte and Lambert (1973)						
Non-selective shunt	50	36	32	22	20	17
Yamamoto et al (1976)						
Non-shunt operation	13	39	30	22	22	18
Warren et al (1982)						
Selective shunt	?	60*	53*	45*	40*	35
Non-selective shunt	?	50*	40*	37*	20*	15*
Rikkers et al (1984)						
Shunt and non-shunt operation†	24	45	35*	30*	20*	17*
Chandler et al (1985)						
Shunt‡	30	36	30	25	20	13
Spence and Johnston (1985)						
Non-shunt operation	25	70	53	38	38	35
Iwatsuki et al (1988b)						
Liver transplantation	302	79	74	71	71	71
Iwatsuki et al						
Liver transplantation (update 1991)	302	80	77	75	74	71

* Value estimated from survival curve.
† Fifteen non-selective shunts, seven selective shunts, and two non-shunt operations.
‡ Both selective and non-selective operations.

procedures for those patients are quite challenging even with recently developed sophisticated methods of portal vein reconstruction (Lerut et al, 1987; Tzakis et al, 1989; Mazzaferro et al, 1990; Stieber et al, 1991). Among the various types of portosystemic shunt operations, the shunts created without hepatic hilum dissection (distal splenorenal shunt and mesocaval H-graft shunt) are more convenient for liver transplantation. However, the incidence of complete portal vein thrombosis after distal splenorenal shunt is approximately 10%, and that of partial thrombosis is approximately 15% (Henderson et al, 1982; Orozco et al, 1988; Spina et al, 1990; Jin and Rikkers, 1991). The thrombosis appears to develop early in the post-shunt period.

Early reports of percutaneous transjugular portosystemic stent shunt (or transjugular intrahepatic portosystemic shunt, TIPS) are promising (Vinel et al, 1985; Richter et al, 1989; Zemel et al, 1991). In this radiological procedure a balloon-expandable, self-expanding metallic stent is placed between the portal vein and the hepatic vein through the hepatic parenchyma. The technical success rate (75% or more) of TIPS and the patency rate (80% or more) of the stent at 1 year are incentives for further clinical trials.

Although further experience and follow-up are needed to confirm the early results of this new technique, TIPS will further diminish the need for a surgical portosystemic shunt, and may revolutionize the treatment of bleeding oesophageal varices.

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