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Liver transplantation in Taiwan: the Chang Gung experience*, **

Chao-Long Chen[1], Kuei-Liang Wang[1], Yu-Ling Hui[2], and Wen-Bin Shieh[3]

[1] Department of Surgery, Chang Gung Memorial Hospital
[2] Department of Anesthesiology, Chang Gung Memorial Hospital
[3] Department of Internal Medicine, Chang Gung Memorial Hospital

Summary. Between March 1984 and February 1991, six orthotopic liver transplantations were performed at the Chang Gung Memorial Hospital in Taiwan. The indications for transplantation were Wilson's disease (5 patients) and biliary atresia (1 patient). Donors and recipients were matched only for size and ABO blood group compatibility, and the recipient operations were performed without the use of a venovenous bypass. Arterial reconstruction was carried out by end-to-end hepatic artery anastomosis (4), thoracic aortic conduit (1), or interposition of an iliac artery graft (1), whereas biliary reconstruction was accomplished by a choledochocholedochostomy using a T-tube stent (4) or a choledochocholedochostomy using an external cholecystostomy without stenting (2). Biliary complications occurred in three patients, and all required additional surgery. The average duration of donor-liver cold ischemia, operating time, and blood loss during surgery were 7 h and 50 min (range, 4.5–9 h), 13.5 h (range, 11.8–17 h), and 4,385 ml (range, 750–12,000 ml), respectively. The immunosuppressive regimens included a cyclosporin-steroid combination (n = 2) and a triple-drug combination (n = 4). All except one of the surviving patients experienced at least one rejection episode that was reversed by a methyl-prednisolone bolus and/or recycle. One patient developed a primary cytomegalovirus (CMV) infection that responded well to Ganciclovir treatment. Two of the patients died, one of injuries sustained in a traffic accident 3 years after transplantation, and the other of massive upper gastrointestinal bleeding. The overall survival value at 3 months was 83%, and the follow-up period ranged from 3 months to 7 years. All of the survivors have achieved complete rehabilitation and currently enjoy an excellent quality of life with normal liver function. Although the present study involved a small number of cases, our results indicate that liver transplantation can be successfully achieved in a high proportion of patients with acceptable morbidity, mortality, and cost in an Asian setting. The extreme shortage of donor organs is currently the most important obstacle limiting the application of liver transplantation in Taiwan.

Introduction

Liver transplantation remains developmental in Taiwan, with a total of only 12 transplants having been performed to date. This paper discusses the six cases operated on at our institution as well as our indications, experiences, and future plans.

A clinical program in liver transplantation was started in Taiwan in 1984 after a period of animal experimentation. The first transplant was performed at Chang Gung Memorial Hospital on March 22, 1984 [2], and was followed by transplants carried out at Veteran's General Hospital on June 17, 1985, and at National Taiwan University Hospital on October 13, 1989. At the beginning of the program, case numbers were small and sporadic, mainly because of very limited organ donations due to the traditional Chinese custom of being buried intact after death. This has recently changed, with 7 of the total of 12 cases having been performed during the past year. This increase has been mainly attributed to enhanced public awareness of organ transplantation and to an increasingly positive attitude toward organ donation.

Between March 22, 1984, and February 10, 1991, 12 orthotopic liver transplants were performed at 3 centers (Table 1). The indications for transplantation included Wilson's disease (n = 6), biliary atresia (n = 2), primary biliary cirrhosis (n = 2), chronic active hepatitis (n = 1),

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Correspondence to: Chao-Long Chen, Department of Surgery, Chang Gung Memorial Hospital at Keelung, 222, Mai-Chin Road, Keelung, Taiwan, R. O. C.

Table 1. Liver transplantation in Taiwan

Date of transplant	Institution	Diagnosis	Survival
March 22, 1984	Chang Gung Memorial Hospital	Wilson's disease	3 years
June 17, 1985	Veterans General Hospital	CAH	25 days
November 3, 1985	Chang Gung Memorial Hospital	Wilson's disease	Alive
August 5, 1989	Veterans General Hospital	Wilson's disease	11 days
October 13, 1989	National Taiwan University Hospital	PBC	28 days
May 21, 1990	Chang Gung Memorial Hospital	Wilson's disease	11 days
August 10, 1990	Chang Gung Memorial Hospital	BA	Alive
October 10, 1990	Veterans General Hospital	Caroli's disease	Alive
November 14, 1990	National Taiwan University Hospital	PBC	Alive
December 8, 1990	Veterans General Hospital	BA	13 days
January 22, 1991	Chang Gung Memorial Hospital	Wilson's disease	Alive
February 4, 1991	Chang Gung Memorial Hospital	Wilson's disease	Alive

CAH, Chronic active hepatitis; PBC, primary biliary cirrhosis; BA, biliary atresia

and Caroli's disease (n = 1). No liver transplantation has thus far been carried out in Taiwan for hepatobiliary malignancy. Our general philosophy is to reserve the very limited and precious donated livers for patients who have a potentially greater chance of being cured. When two candidates of similar size and the same blood group are competing for a donated liver, we tend to select the one with benign end-stage liver disease, particularly at the beginning of our program. As our experience increases and organ donation becomes more acceptable, we will expand our indications to include malignant liver disease with no evidence of extrahepatic spread. In particular, patients with relatively small or multicentric hepatomas in severely cirrhotic livers, who cannot be treated by conventional subtotal resection, are considered to be candidates for transplantation.

Patients and methods

Patients. Patients referred for transplantation were accepted as suitable candidates on the basis of proven irreversible, progressive liver disease responsible for (1) an estimated survival of less than 1 year, (2) an unacceptable quality of life, or (3) imminent death. Absolute contraindications for transplantation included (1) active sepsis outside the hepatobiliary tree, (2) malignancy outside the liver, and (3) advanced cardiopulmonary disease. Donors and recipients were matched only for size and ABO blood group compatibility.

At Chang Gung Memorial Hospital, six patients (three men and three women) underwent liver transplantation between March 22, 1984, and February 10, 1991. Their ages ranged from 9 to 38 years (mean, 21.5 years). The indications for liver transplantation were Wilson's disease in five patients and biliary atresia in one patient. One patient was transplanted soon after she had been resuscitated from shock and hepatic coma due to esophageal variceal bleeding associated with a prothrombin time of 39.6 s (normal control value, 10.6 s). The child with biliary atresia had previously undergone a Kasai operation.

Surgical technique. Donor hepatectomy was performed by standard techniques [6], often in conjunction with multiple organ procurement, including the kidneys and heart. Since 1990, UW solution has been used as a substitute for Collin's solution for liver preservation. Hepatic homografts were procured using an in situ flush technique and were stored in a cold preservation solution. Both donor and recipient operations were carried out by the same surgeon.

The recipient operation was performed using an inverted T incision and a Kent retractor to provide exposure. Before removal of the native liver, trial clamping of the vena cava was done. This was tolerated well by all patients without a venovenous bypass. The order of anastomosis was suprahepatic vena cava, infrahepatic vena cava, portal vein, hepatic artery, and bile duct. Hepatic artery-to-artery anastomosis was used whenever the vessel size and quality were adequate. An aortic Carrel patch of the donor celiac axis was anastomosed to a branch patch of the proper hepatic-gastroduodenal bifurcation in three patients and to a branch patch of the hepatic bifurcation in one patient. In another patient, a segment of the donor thoracic aorta was anastomosed to the recipient's abdominal aorta, and in another case, a segment of the iliac artery was used for an interposition graft to bridge the gap between the homograft celiac axis and the recipient's abdominal aorta. Biliary reconstruction in the six recipients with normal bile ducts (including the biliary atresia patient, whose native CBD was patent) involved a choledochocholedochostomy with a T-tube stent in four cases and a choledochocholedochostomy using an external cholecystostomy without stenting in the other two cases.

Immunosuppression. Cyclosporin and prednisolone served as the principal immunosuppressive regimen. Since 1990, a triple drug immunosuppressive regimen (cyclosporin, azathioprine, and prednisolone) has been used to take advantage of immunosuppressive synergy. Initial immunosuppression was achieved using intravenous methylprednisolone and azathioprine, with cyclosporin being introduced on the 3rd day if there was no renal failure. Intravenous cyclosporin was switched to oral therapy after the return of normal bowel function. Attempts were made to maintain the whole blood level of cyclosporin at between 200 and 400 μg/ml by monitoring with monoclonal specific radioimmunoassay. Azathioprine was discontinued at 3 months after transplantation, whereas cyclosporin and prednisolone were continued indefinitely.

Rejection episodes were treated with a bolus of intravenous methylprednisolone and/or an increasing cyclosporin dose and/or reinstitution of a 5-day recycle of intravenous methylprednisolone.

Results

The cold ischemia time of the donor livers achieved by cold storage in Collin's solution (n = 2) or UW solution (n = 4) ranged from 4 h and 34 min to 9 h (average, 7 h and 50 min). The function of the six grafts was immediate following revascularization, with bile flow becoming evident intraoperatively. The operating time for liver transplantation ranged from 11 h and 45 min to 17 h (average, 13 h and 34 min). Blood loss during surgery ranged from 750 to 12,000 ml (average, 4,385 ml). Patients with profound preoperative coagulopathy lost significantly more blood.

Four of the six patients are currently alive after transplantation, with the follow-up periods ranging from 3 months to 7 years. Overall survival at 3 months after transplantation was 83%. All of the survivors have since returned to full and active lives, each showing good liver function. However, two patients died. Our first patient, who represented the first successful liver transplant in Asia and had gone back to gainful employment, was struck by a truck while riding a motorcycle on her way to work; this fatal accident happened at 3 years after transplantation. The other mortality occurred 11 days posttransplant due to massive upper gastrointestinal bleeding. All except one of the patients who survived for longer than 1 month experienced at least one rejection episode; all episodes were reversed by a methylprednisolone bolus and/or recycle. OKT3 was not used in our patients.

Hypertension, the most commonly encountered complication in the ICU, was present even in patients who were not treated with immediate postoperative cyclosporin. BP control was achieved using hydralazine, a beta-blocker, or, less commonly, nitroprusside infusion. The hypertension usually resolved within 2–3 months.

Biliary complications occurred in three patients, and all required additional surgery. Biliary sludge-cast formation in one patient was treated by a left lateral segmentectomy followed by postoperative choledochoscopic removal of retained biliary casts [3]. Stenosis of the biliary anastomosis in one patient with a choledochocholedochostomy was converted to a Roux-en-Y choledochojejunostomy. The development of a CBD stone at 4 years after transplantation in one patient required a choledocholithotomy.

All prospective recipients were routinely tested for the presence of anti-CMV antibodies and were designated as CMV-positive or CMV-negative. Our only CMV-negative recipient received a liver from a CMV-positive donor. This patient developed severe CMV sepsis that manifested as a spiking high fever along with leukopenia, mild jaundice, and very high cannilicular enzymes at 5 weeks posttransplant. The diagnosis was based on the appearance of anti-CMV antibodies (IgG an IgM), positive blood cultures, and the presence of characteristic CMV inclusion bodies on liver biopsy. This patient responded well to Ganciclovir treatment.

The total cost for the initial hospitalization of our patients ranged from U.S. $22,222 to $ 74,074 (average, $ 47,530). Because of the experimental status assigned by the National Health Administration, no insurance company was willing to pay for liver transplantation. The expenses were covered by the Chang Gung Medical Research Grant.

Discussion

Orthotopic liver transplantation is becoming well accepted as a therapeutic modality for selected patients with advanced, irreversible liver disease. A new liver transplantation program provides not only a dramatic therapeutic option but also an academic stimulus to the entire hospital.

The first liver transplant in Taiwan was performed in 1984, when the concept of brain death had not yet been legally approved. That first operation was performed in an emergency, life-saving situation soon after the recipient had been resuscitated from shock and hepatic coma due to esophageal variceal bleeding associated with a profound coagulopathy. The donor liver was obtained from a heart-beating, brain-dead cadaver. This drew extensive discussion and criticism from the medical profession. Fortunately, the patient recovered, and the concept of brain death became a topic of heated discussion in the media among medical professionals as well as the lay public. After much debate, a consensus on brain death was reached in the medical community at 7 months following the first liver transplantation; 3 years later, in 1987, the Human Organ Transplant Act was passed in the Congress and officially proclaimed by the President. The concept of brain death was then legally defined and accepted.

Due to refinements of the surgical techniques and to increased experience, vascular and biliary reconstructions can be performed safely and effectively. Nevertheless, liver transplantation remains a formidable procedure, and all of our patients experienced one or more nonlethal postoperative complications. Four of our six recipients required an additional surgical procedure following the transplantation; this incidence is higher than the 40%–50% value reported by the most established centers [1, 7].

Our survival value of 83% at 3 months, which was obtained during follow-up period ranging from 3 months to 7 years and compares favorably with those reported by other investigators [4, 8], demonstrates that liver transplantation can be performed with acceptable morbidity, mortality, and cost in an Asian setting. Since a majority of deaths occur during the first 3 months following liver transplantation, survival beyond this period is usually sustained [5]. This adds credibility to the present survival data, although the most recent cases are in the early stage of recovery. The condition of the five survivors is particularly encouraging; all have returned to full and active lives. The excellent quality of life and complete rehabilitation of these patients provides ample reward for the time, effort, and expense required for liver transplantation.

Currently, the most important obstacle limiting the application of liver transplantation in Taiwan is the dire shortage of donor organs. The scarcity of donor organs continues to be a dilemma for recipients urgently requiring liver transplantation. People are generally reluctant to donate the organs of beloved ones or their own. This concept is more a product of tradition and custom than of religion. People are inclined to wish to keep their body intact after death because they tend to misapply old sayings such as the following from Confucius: "In order to pay respect to your parents, you should not damage even your hair or skin."

Greater awareness by both the public and the medical profession of the need for donors and improvement of the organ procurement organizations are ways of alleviating this problem of organ shortage. An organ procurement agency was established at Chang Gung Memorial Hospital in January 1991 to improve the public attitude and behavior regarding organ donation through public education and communication and to increase the availability of donor organs through interinstitutional coordination and transportation.

In conclusion, we feel that in light of the scarcity of organ donors, our decision to accept only end-stage liver disease patients with a high expectation of being cured has paid off nicely in the silencing of medical sceptics, in recognition by the public, and in an increasing availability of donor organs.

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