Evaluation of the first 100 liver transplantations

İlk 100 karaciğer transplantasyonu değerlendirilmesi

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Background/aims: *We aimed to present the experience of the first 100 liver transplantations carried out at Akdeniz University.* ***Methods:*** *The data of 100 patients in pediatric and adult age groups who underwent liver transplantation at Akdeniz University Organ Transplantation Center between January 2000 and January 2007 were examined retrospectively. The cases between January 2000 and December 2003 were evaluated as the first term and those between January 2004 and January 2007 as the second term.* ***Results:*** *The mean age of the 100 patients (52M, 48F) was 38.6±17.3 (1-68) years. One-year and three-year survival rates of the patients were determined as 67.3% and 54.3% in the first term and 88.7% and 79.3% in the second term, respectively.* ***Conclusions:*** *With better comprehension of recipient and donor surgery technique, in addition to accumulation of knowledge and experience, the results in liver transplantation might be improved.*

Key words: Liver, transplantation, experience

Amaç: *Akdeniz Üniversitesinde gerçekleştirilen ilk 100 karaciğer transplantasyonu deneyiminin sunulması amaçlandı.* ***Yöntem:*** *Akdeniz Üniversitesi Organ Nakli Merkezinde Ocak 2000 ile Ocak 2007 tarihleri arasında pediatrik ve yetişkin yaş grubunda karaciğer nakli yapılan toplam 100 hastanın verileri retrospektif olarak incelendi. Olgular Ocak 2000 ile Aralık 2003 tarihleri arası birinci dönem ve Ocak 2004 ile Ocak 2007 tarihleri arası ise ikinci dönem olarak değerlendirildi.* ***Bulgular:*** *% 52'si erkek, % 48'i kadın olan hastaların yaş ortalaması 38,6±17,3 (1-68) idi. 1 ve 3 yıllık hasta sağkalım oranları sırası ile ilk dönemde % 67.3 ile % 54.3 iken ikinci dönemde % 88,7 ile %79.3 olarak tespit edildi.* ***Sonuç:*** *Alıcı ve donör cerrahisi tekniğinin daha iyi anlaşılmasına ek olarak yeterli bilgi ve tecrübe birikimi ile birlikte karaciğer transplantasyonu sonuçları daha iyi olabilmektedir.*

Anahtar kelimeler: Karaciğer, transplantasyon, deneyim

INTRODUCTION

The first liver transplantation was carried out by T.E. Starzl in 1967 (1). After overcoming difficulties of organ supply, preservation and immunosuppression, it has become the most important treatment option in end stage liver disease (2). Although in recent years the number of centers performing liver transplantations has significantly increased, the desired numbers have not yet been reached and many patients on donor waiting lists die. According to the United Network of Organ Sharing (UNOS), 10 patients on waiting lists die each day (3). The one-year survival rate, reported by liver transplantation centers as approximately 30% in the beginning, now approaches nearly 90% with the implementation of appropriate surgical techniques, effective immunosuppression and sufficient postoperative intensive care unit support (4). We present herein the short- and long-term results of the first 100 patients in pediatric and adult age groups with

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end stage liver disease to have undergone liver transplantation from cadaveric or living donors since the liver transplantation program was started in our center, in January 2000.

MATERIALS AND METHODS

The data of 100 patients in pediatric and adult age groups who underwent liver transplantation at Akdeniz University Organ Transplantation Center between January 2000 and January 2007 were examined retrospectively (Table 1). The cases transplanted between January 2000 and December 2003 were evaluated as the first term and those between January 2004 and January 2007 as the second term. All operations were carried out by the same surgical crew. While en-block technique is preferred at our center, split liver transplantation was recently performed in a total of 10 cases. All grafts were perfused with University of Wisconsin solution. Operation methods used included piggy-back, conventional and Auxiliary Partial Orthotopic Liver Transplantation (APOLT). Reconstruction of the bile duct was performed with duct-to-duct anastomosis with or without T-tube or Roux-en-Y choledochojejunostomy. For patients with hepatitis B (HBV) cirrhosis, 2000 IU HBV-specific immunoglobulin (Hepatect CP flacon, Kansuk, Turkey) was applied in the non-hepatic phase. Immunoglobulin treatment was continued with lamivudine to maintain anti-Hbs anticore titer over 100 IU/L. As immunosuppressive treatment, 0.1-0.15 mg/kg/day tacrolimus or 6-8 mg/kg/day cyclosporine, and 1-2 g/day mycophenolate mofetil (MMF) was used in addition to prednisolone in select cases. Patient deaths within postoperative 30 days were accepted as operative mortality. Kaplan-Meier statistical method was used to calculate patient survival.

RESULTS

Ninety-six of the transplanted livers were cadaveric and four were from living donors. Mean age of the recipients was 38.6±17.3 (1-68) years, while mean age of the donors was 31.5±13.4 (6-62) years. Fifty-eight of the patients were male and 42 female, and 20 were in the pediatric age group. Fifty-five of the patients were blood type A, 19 type B, 23 type 0 and 3 type AB. The reasons for hepatic failure were mostly viral hepatitis, alcoholic cirrhosis and cryptogenic cirrhosis (Table 2). According to Child-Pugh scoring system, 9% of the patients were evaluated as A, 41% as B and 39% as C. In eight cases (8%), emergency transplantations were performed due to fulminant hepatitis. Of the other three cases (3%), metabolic liver disease was the indication in two cases and hemangioendothelioma in one case. En-block transplantation was performed for 90 patients and split liver transplantation for 10 patients. Operation method included piggy-back in 59 cases, conventional in 40 cases and APOLT in one case. Mean cold ischemia duration was 5.42±2.17 (2-10) hours. Bile duct anastomosis was performed with duct-to-duct method in 71 cases and with Roux-en-Y choledochojejunostomy in 24 cases. In five cases with perioperative mortality, bile anastomosis could not be

Table 1. Demographic and operative data of liver transplantation patients

	1st Term (n=47)	2nd Term (n=53)	p
Age	40.7±17	36.1±17	0.18
Sex (Male/Female)	32/15	26/25	0.06
Age of donor	33 ±14	29±12	0.07
Cold ischemia (hour)	5.7±2.4	5.0±1.8	0.11
Type of transplantation (right lobe/left lobe/total)	1/1/45	0/8/45	
Transplantation Technique			
Piggy-back	26	33	
Conventional	21	19	
APOLT*	-	1	
Type of bile anastomosis			
Roux-en Y hepaticojejunostomy	10	14	
Choledochocholedochostomy	34	37	
Reoperation	15	18	
Operative mortality	14	6	0.02**
Patient survival rate			
1 year	67.3%	88.7%	
3 years	54.3%	79.3%	
Stay at hospital (day)	21±19.75	17.7±15.06	

* Auxiliary Partial Orthotopic Liver Transplantation, ** $p<0.05$

completed. In 61 of the patients with duct-to-duct anastomosis, T-tube was used.

Hepatocellular carcinoma was diagnosed in five patients, partial portal vein thrombosis was observed in six patients and splenic artery aneurysm was identified in one patient, perioperatively. Renal transplantation was performed spontaneously during liver transplantation in a total of three patients (2 with oxalosis, 2 with nephronophthisis); splenectomy was performed in one patient due to splenic artery aneurysm; and total gastrectomy was performed in one patient due to gastric carcinoid tumor. Retransplantation was performed in two cases with chronic rejection and primary nonfunction graft.

As immunosuppression, apart from 20 cases with operative mortality, tacrolimus (combined with MMF in 24 cases) was prescribed for 53 patients and cyclosporine (combined with MMF in 15 cases) for 27 patients. The treatment was switched to m-TOR inhibitors in three patients because of serious calcineurin toxicity. Posttransplant diabetes mellitus was observed in 10 patients. Six of these patients were using tacrolimus and four cyclosporine. The treatment of three patients using tacrolimus was switched to cyclosporine, while for the other three patients, insulin treatment was ended as blood glucose levels were adjusted. There was no drug switch for cyclosporine-administered patients and two of them use insulin now. Of 43 patients with acute rejection, 15 (33.3%) were treated with anti-thymocyte globulin (ATG) and 28 (66.7%) with pulse steroid.

Of 33 patients reoperated in the early and late postoperative periods, eight had intraabdominal bleeding, six had bile leakage, 14 had vascular complications, one had intraabdominal abscess, two had incisional hernia and two had ileus. In the perioperative evaluation of 14 patients who had vascular impairment determined by postoperative Doppler ultrasound, hepatic artery thrombosis was observed in eight patients, and reconstructions with or without grafts were performed. No pathology was observed in the other six cases. During the long- term follow-up, bile leakage occurred in five patients after T-tube was removed; three of them were operated and treated with primary suture and the other two patients were treated with nasobiliary drainage. Of the patients with bile anastomosis stricture, three were treated with endoscopic retrograde cholangiopancreatography and two with biliary stents that were placed percutaneously. The most frequent medical complications observed in the early and late postoperative periods were determined as respiratory (n=13), cardiovascular (n=12), neurological and psychiatric (n=9), malignancy (n=4), acute and chronic renal failure (n=10), posttransplant diabetes mellitus (n=10), ascites responsive to medical treatment (n=7), and bile anastomosis stricture (n=15).

Table 2. Indications for liver transplantation

	n
HBV cirrhosis	31
HCV cirrhosis	11
Cryptogenic cirrhosis	10
Alcoholic cirrhosis	16
Fulminant hepatitis	8
Wilson cirrhosis	6
Congenital hepatic fibrosis	5
Primary biliary cirrhosis	2
Secondary biliary cirrhosis	2
Oxalosis	2
Other	7

In the first term, 14 (29.78%) of 47 patients died during the operative period and 10 (21.27%) died during the follow-up period. In the second term, 6 (11.3%) of 53 patients died during the operative period and 5 (9.4%) died during the follow-up period. A significant difference in operative mortality was determined between the two periods (p=0.02). Causes of death during the perioperative period were hepatic artery thrombosis (n=8), intraabdominal bleeding (n=4), primary nonfunction test (n=4), myocardial infarction (n=2), and biopsy-proven acute rejection (n=2). The most frequent cause of death during the follow-up period was cardiopulmonary disease. Other causes were determined as sepsis, recurrence of hepatocellular carcinoma, chronic rejection, Kaposi's sarcoma, recurrence of hepatitis C virus (HCV), posttransplant lymphoproliferative disease (PTLD) and suicide. Mean follow-up durations for each period were 57.5±7.8 and 28.8±2.2, respectively. One-year and three-year survival rates of the patients were determined as 67.3% and 54.3% in the first term and as 88.7% and 79.3% in the second term, respectively.

DISCUSSION

Although liver transplantation is one of the most complicated surgical approaches, it can be a life-saving procedure in patients with end stage liver disease. The first experimental liver transplanta-

tion was performed by Moore in 1959. Liver transplantation in humans was first attempted by Starzl in 1963, but the first successful liver transplantation was performed by the same surgeon in 1967 (1). One hundred liver transplantations have been performed at the Akdeniz University Organ Transplantation Training, Research and Application Center since January 2000. Since that date, 1100 kidney, 37 pancreas and 17 heart transplantations have been performed at our center. Although mostly en-block liver transplantation with cadaver origin is preferred, liver transplantations from living donors have been favored over the last one year (Table 1).

Indications for liver transplantation are divided into four main groups as chronic and acute hepatic failure, primary liver malignancies that cannot be treated with conventional resection, and metabolic diseases due to enzyme defects without parenchymal liver disease. The most frequent reasons for chronic hepatic failure are autoimmune and viral hepatitis and alcoholic and congenital liver diseases. Among the first 100 patients who underwent liver transplantation, HBV cirrhosis was the most frequent indication, at a rate of 31%. Disease recurrence after the transplantation might be an important problem in these patients. Thus, in order to reduce viral replication, we start hepatitis B immunoglobulin treatment in the non-hepatic phase and use it for at least one year in combination with lamivudine. In this patient population, in whom we aimed to maintain anti-Hbs anticore titer above 100 IU/L, there was no HBV recurrence to date. However, two of 11 patients who underwent liver transplantation due to hepatitis C cirrhosis had HCV recurrence. Although psychiatric aid was given in the postoperative period to 16 patients who underwent liver transplantation due to alcoholic liver disease, one patient resumed alcohol consumption.

In the initial years of our transplantation program, we performed transplantations to senior patients with poor general condition because our waiting list and options were limited, so we generally used conventional technique in this patient group. As our waiting list expanded in time, we had the opportunity to perform transplantations to patients in better general condition. We began to use the piggy-back technique, which is cheaper and preferred worldwide, in this group of patients (6).

The most common techniques for reconstruction of the bile duct in liver transplantations are performed with duct-to-duct anastomosis with or without T-tube or Roux-en-Y choledochojejunostomy with or without stent (7). Both techniques have been used in our center. In the second term, bile peritonitis occurred after removing the drainage in five cases where choledochocholedochostomy was performed by means of T-tube. T-tube provides an opportunity to prevent posttransplant early stage bile leakage and helps to follow bile quantity, but it may also cause serious morbidity during the removal of drainage. Hence, we currently prefer not to use T-tube at the anastomosis of choledochocholedochostomy.

Overall, one-year survival rate was determined as 75.4% and three-year survival rate as 64.1% in our series. When the data were examined separately according to the terms, one-year and three-year survival rates were determined as 67.3% and 54.3% in the first term and as 88.7% and 79.3% in the second term, respectively. Although survival rates were relatively higher in the second term, the increase was not statistically significant ($p=0.08$). The reason for this is the mean follow-up duration of 28.8 months in the second term. Furthermore, although a program for liver transplantation from living donors was started in the second term, operative mortality rates have significantly decreased ($p=0.02$). Causes of death in the postoperative period were primarily vascular problems, bleeding, primary nonfunction, acute rejection, cardiological problems due to overage and sepsis. Long-term patient deaths were mostly caused by cardiopulmonary failure, sepsis, and central nervous system metastasis of hepatocellular carcinoma recurrence.

In conclusion, liver transplantation is a complicated surgical approach in patients with end stage liver failure and can only be performed in certain centers. Orthotopic liver transplantation can be performed only in a few centers in our country. Although one-year and three-year survival rates of liver transplantation performed in the first term were low, second term results and especially operative mortality rates significantly improved in conjunction with our increasing experience.

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