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Experience of Orthotopic Liver Transplantation in 11 Patients with Liver Cirrhosis from Korea
: Medical Factors Affecting Outcome

Orthotopic liver transplantation (OLT) has evolved to become a standard treatment of choice for end-stage liver diseases. The present study was performed to evaluate the peri-operative medical factors affecting transplantation outcome and to determine if patients with type B viral cirrhosis were acceptable for OLT. A total of 11 patients with end-stage cirrhosis, who have received OLT in Kangnam St. Mary's Hospital since May 1993, included 8 HBV-related cases, 1 Hepatitis C Virus (HCV)-related case, and 2 non-B, non-C cases. One-year cumulative survival rate by Kaplan-Meier method was 43.7%. Factors significantly associated with 1-year survival of the recipients during pre-OLT period were performance status and modified Pugh-Child score (p=0.015 and p=0.015, respectively). Among those 4 patients who lived longer than 1 year, 3 of 4 patients with HBsAg-positive had no HBV re-infection with our protocol. These results suggest that, to improve the outcome of OLT in cirrhosis patients, transplantation should be performed in the stage when patients maintain better performance and hepatic functional reserve during the end-stage of liver cirrhosis. In addition, patients with cirrhosis caused by HBV infection may be indicated for OLT, because HBV re-infection is preventable effectively with a high-dose hepatitis B immunoglobulin protocol.

Key Words : *Liver transplantation, orthotopic; Liver cirrhosis; Hepatitis B virus; Hepatitis C-like viruses*

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INTRODUCTION

During the early period of orthotopic liver transplantations (OLT) after the first OLT was performed by Starzl in March 1963 (1), OLT was not so popular because its success rate was less than 30%. However, it has become the therapy for patients with acute or chronic hepatic failure (2-4), and this success has been achieved through improvement of surgical technique, organ preservation, and peritransplant care as well as by the adjuvant of highly effective immunosuppressive agents such as cyclosporin A and FK506. Currently, actuarial survival rate at 1 and 5 years are as high as 90% and 64% (5), so that most patients who undergo OLT in the USA can be expected to survive the immediate postoperative period and can enjoy a considerably improved quality of life.

OLT is indicated in patients with severe liver disease, including fulminant hepatic failure, cirrhosis, serious congenital hepatobiliary disease, and inherited metabolic liver diseases (6). However, hepatitis B virus (HBV) infection has been considered to be one of the relative contraindications to OLT because of both the high recurrence rates and poor survival rates after transplantation (7). The prohibitive cost of maintaining these patients under hepatitis B immune globulin (HBIG) therapy is another drawback.

Nevertheless, in Korea, where HBV infection is the most important etiologic factor in cirrhosis and hepatocellular carcinoma, a total of 92 patients have received OLT since 1988 (46 patients have survived; approximately a 50% survival rate) (not published but privately collected data). In the present study, we have assessed the value of perioperative variables in predicting the outcome of OLT.

MATERIALS AND METHODS

Patients

Since May 1993, a total of 11 patients with liver trans-

plants have been treated at the Department of Internal Medicine, Kangnam St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea.

Recipients

Inclusion criteria for the recipients were the same as those described elsewhere (8). At registration, recipients were systematically evaluated and then monthly by a pre-established protocol until OLT. A computerized tomogram we performed in all cases within 6 months of OLT to screen out hepatocellular carcinoma and to evaluate the severity of collateral vessels. An ultrasonogram was performed just before transplantation to evaluate the possible presence of hepatocellular carcinoma and severity of collaterals and ascites. The informed consent was obtained at registration and again just before transplantation, after all possible problems related to the operation have been explained.

Donors

Brain death was confirmed by at least two doctors of Department of Neurology and Neurosurgery with criteria suggested previously (9). Additionally, to determine whether the patient was a good candidate as a liver donor, all the features were evaluated systematically by the donors' criteria described elsewhere (10). Hospital ethics commitee was held three times immediately before transplantation.

Surgery

The transplant technique was similar to standard technique, using venovenous bypass and end to end biliary anastomosis as described by Starzl (11). Only one case had end-to-side choledochojejunal anastomosis.

Immunosuppressive therapy

A combination of cyclosporin A (Sandimun II™, Sandoz, USA) and corticosteroid was used as a standard immunosuppressive therapy to prevent graft rejection. One patient received OKT3 due to steroid-resistant acute rejection for 7 days in the early postoperative period.

Antibiotic therapy

All patients received acyclovir and sulperazone throughout the perioperative phase.

Hepatitis B immunoglobulin (HBIG)

To prevent HBV recurrence, a high dose protocol of polyclonal HBIG derived from plasma (Green Cross, Suwon, Korea) was administered in all HBsAg-positive recipients by intravenously infusion; 10,000 IU during anhepatic phase, 10,000 IU daily for day 1 through 7, and then 10,000 IU once or twice a month to maintain antibody level above 100 IU/ml.

Follow-up evaluation

The patients were followed-up monthly with a complete hemogram, biochemistry, and systemic review of symptoms and physical signs.

Serology

Hepatitis B surface antigen (HBsAg), anti-HBs antibody, hepatitis B e antigen (HBeAg), antibody to HBeAg (anti-HBe), total antibody to hepatitis B core antigen (anti-HBc), and alpha-fetoprotein (AFP) in serum were tested using respective radioimmunoassay kit (Abbott Laboratories, Chicago, Il, USA). Antibody for hepatitis C virus (HCV) in serum was tested with a second or third-generation enzyme immunoassay kit (Abbott Lab.).

Polymerase chain reaction (PCR)

HBV DNA was detected in serum samples by PCR with primers derived from precore-core region of HBV genome. HCV RNA in serum was detected by reverse transcription-nested PCR (RT-PCR) with primers derived from 5'-untranslated region of HCV cDNA genome according to the protocol described elsewhere (12).

Variables analyzed in this study

To analyze the medical aspect of parameters influencing the outcome of OLT, variables were selected from clinical and laboratory tests determined at pre-OLT and also during post-OLT 7 days. These included a performance score (13), a modified Pugh-Child score (14), ascites, encephalopathy, variceal bleeding, spontaneous bacterial peritonitis (SBP), hepatorenal syndrome (HRS), nutritional status (15), blood chemistry, complete hemogram, and urinalysis. Surgical and other technical factors were not included in this analysis.

Statistical analysis

To identify factors significantly related to the survival, Fisher's-Exact test was done. One-year cumulative survival rate was expressed according to Kaplan-Meier method. The mean values of laboratory data between long-term and short-term survivors were compared with unpaird *t*-test. A probability value of less than 0.05 was considered to be statistically significant.

RESULTS

Patients' profiles

All patients were male with a median age of 45 years (range 16-58 years). All patients had cirrhosis caused by

Table 1. Patient's profiles

List	Age	Sex	HBsAg	HBeAg	Anti-HBc	Anti-HCV	HBV DNA*	HCV RNA†	Modified Pugh-Child score‡	Pugh-Child grade	Performance status§	Cirrhosis‖
1	28	Male	+	−	+	−	+	−	7	B	0-1	macronodular
2	44	Male	+	−	+	−	+	−	10	C	3	macronodular
3	57	Male	−	−	−	−	−	−	12	C	4	macronodular
4	45	Male	−	−	−	+	−	+	7	B	1-2	micronodular
5	37	Male	−	−	−	−	−	−	11	C	3-4	micronodular
6	56	Male	+	+	+	−	+	−	9	B	2-3	mixed
7	18	Male	+	+	+	−	+	−	12	C	3-4	mixed
8	26	Male	+	+	+	−	+	−	12	C	4-5	macronodular
9	48	Male	+	−	+	−	+	−	11	C	3-4	macronodular, HCC¶
10	45	Male	+	+	+	−	+	−	7	B	1-2	macronodular
11	45	Male	+	+	+	−	+	−	10	C	3	micronodular

*HBV DNA was detected in serum by polymerase chain reaction.
†HCV RNA was detected in serum by reverse transcription-nested polymerase chain reaction (12).
‡Pugh-Child score was determined by a modified method (14).
§Performance status was determined by a modified method (13).
‖Cirrhosis was determined by visual observation after removal of liver.
¶This case had small hepatocellular carcinoma in liver surface, which was not found by radiologic examination during pre-OLT period.

HBV infection (8 cases), HCV infection (1), or non-B, non-C agent(s) (2) (Table 1).

By visual observation after removal of liver, 5 patients with HBsAg had macronodular cirrhosis, 3 patients had micronodular cirrhosis (1 HBsAg-positive, 1 anti-HCV-positive, and 1 non-B, non-C patients), and 2 patients had mixed nodularity (2 HBsAg-positive).

Survival rate

Five patients have survived over 1 year; 1 patient died at post-OLT 23 months and 4 patients are still alive (between 24 and 42 months at the present time). One-year cumulative survival rate was 43.7% by Kaplan-Meier method.

Causes of death

Among 7 mortalities, 6 died within 58 days and one died 23 months after transplant (Table 2).

The cause of death in the six survivors under 1 year were sepsis (n=3, 50%), hepatic artery thrombosis (n=1), metabolic encephalopathy of unknown origin (n=1), and massive bleeding from tearing of IVC (n=1).

One survivor over 1 year died of progressive idiopathic non-functioning liver associated with intractable ascites and hepato-renal syndrome. By autopsy analysis, no cirrhosis could be observed grossly and microscopically, but massive necrosis of unknown origin was identified by microscopic observation.

Table 2. Outcome of orthotopic liver transplantation

List	Dead or alive	Duration of survival	Groups of survivor*	Reactivation of hepatitis viruses	Causes of death
1	Alive	49 months	A	No	
2	Death	23 months	A	Hepatitis B	Hepatorenal failure
3	Death	4 weeks	B	-	Sepsis
4	Alive	28 months	A	Hepatitis C	
5	Death	5 weeks	B	-	Sepsis
6	Alive	28 months	A	No	
7	Death	2 weeks	B	-	Hepatic artery thrombosis
8	Death	4 weeks	B	-	Sepsis
9	Death	8 weeks	B	-	Metabolic encephalopathy
10	Alive	23 months	A	No	
11	Death	1 day	B	-	Operative bleeding

* Group A: Survivors over 1 year; Group B: Survivors under 1 year.

Table 3. Complications after transplantation

Complications within Post-OLT 1 month	No. of cases	Complications after Post-OLT 1 month	No. of cases
Acute renal failure	10	Mild hypersplenism	5
Ascites	10	Peripheral neuropathy	4
Acute rejection	4	Mild elevation of Cr	3
Psychosis	3	Gingival hypertrophy	2
Pleural effusion	2	Depression	2
Cholestasis	2	Diabetes mellitus	2
Biliary leakage	1	Bile duct stone	1
		Hypertension	1
		Ascites	1
		Herpes Zoster infection	1
		Ventral hernia	1

Complications

Complications encountered within 30 days of transplantation were acute renal failure, ascites, psychosis, acute rejection, pleural effusion, severe cholestasis of unknown origin, pleural effusion, and leakage of biliary anastomosis (Table 3).

Complications seen later than 30 days posttransplant were mostly those related to the use of cyclosporin A and steroids, but recurrent cholangitis associated with biliary stone was observed in one case (Table 3).

Variables related to survival

Five survivors over 1 year maintained the good performance status (score 0-1 of 6), while 5 of 6 survivors under 1 year were in the poor performance state (score 3, 4 or 5 of 6; $p=0.015$). Four survivors over 1 year maintained Pugh-Child B grade hepatic function (7-9), while all 6 survivors under 1 year were in the Pugh-Child C grade (score 10, 12, or 13; $p=0.015$) (Table 4).

Among laboratory data, no variables during pre-OLT period were helpful for predicting outcome, while during post-OLT 7 days only total serum bilirubin and blood urea nitrogen (BUN) were important (104.7 ± 23.39 mg/dl vs. 38.3 ± 10.69 mg/dl in BUN and 11.5 ± 4.56 mg/dl vs. 3.8 ± 2.4 mg/dl in total bilirubin; $p=0.002$ and $p=0.01$, respectively) (Table 5).

Re-infection of hepatitis viruses

Among 8 HBsAg positive patients, survivors over 1 year were 4. Of them, 3 are currently alive with no evidence of reinfection of HBV. One transplant was re-infected with HBV, developed chronic hepatitis B, and resulted in progressive idiopathic liver failure with intractable ascites.

The patient who tested positive for anti-HCV antibody prior to transplantation was reinfected with HCV 2 weeks posttransplant, and developed chronic hepatitis C

Table 4. Variables affecting to outcome: clinical data

	Survivors under 1 yr. (n=6)	Survivors over 1 yr. (n=5)	Significance
Pre-OLT			
Encephalopathy	6	2	NS*
Intractable ascites	3	1	NS*
Gastrointestinal bleeding	1	2	NS*
Subacute bacterial peritonitis	4	2	NS*
Hepatorenal syndrome	1	3	NS*
Performance status (4-6)	5	0	p=0.015*
Pugh-Child score (10-15)	6	1	p=0.015*
Post-OLT 7 days			
Infection	3	2	NS*
Acute renal failure	5	4	NS*
Pleural effusion	5	4	NS*
Acute rejection	2	2	NS*

* Fisher's-Exact test was applied to evaluate the significance of clinical data as a prognostic factor.

Table 5. Variables affecting to outcome: laboratory data

	Pre-OLT		Significance	Post-OLT		Significance
	Suvivors under 1yr	Survivors over 1yr		Survivors under 1yr.	Survivors over 1yr	
BUN (mg/dl)	32.3±13.8	18.6±10.3	NS*	104.7±23.39	38.3±10.69	p=0.002*
Creatinine (mg/dl)	1.3±0.81	0.9±0.19	NS*	3.1±1.33	1.0±0.18	NS*
Total bilirubin (mg/dl)	10.6±14.88	5.1±6.03	NS*	11.5±4.56	3.8±2.4	p=0.01*
Albumin (g/dl)	2.5±0.33	2.9±0.45	NS*	2.5±0.33	2.9±0.45	NS*
AST (IU/L)	78.8±34.59	75.2±47.71	NS*	53.6±15.7	26.0±10.29	NS*
ALT (IU/L)	49.1±30.15	50.0±26.20	NS*	133.6±76.8	128.0±138.8	NS*
Alkaline phosphatase	406±239.4	291±100	NS*	255.6±52.73	203.5±66.74	NS*
r-GT	51.1±20.92	48.2±1.01	NS*	78.2±25.8	89.5±38.25	NS*
Prothrombin time (%)	48.8±16.2	45.2±16.43	NS*	84.8±16.3	89.8±10.0	NS*
Total cholesterol (mg/dl)	72.5±11.38	131.0±87.30	NS*	126.3±8.08	122.5±16.26	NS*
Triglyceride (mg/dl)	44.5±31.77	41.75±19.63	NS*	176.3±14.43	142.5±9.19	NS*
Hemoglobin (g/dl)	9.4±1.87	9.9±1.77	NS*	10.6±0.56	10.4±1.08	NS*
Wbc (mm^3)	3.8±1.52	4.2±2.53	NS*	4.5±2.1	4.9±1.92	NS*
Platelet ($10^3/mm^3$)	54.8±36.7	65.8±33.4	NS*	50.4±18.9	66.4±22.68	NS*
α-fetoprotein (ng/ml)	5±7.25	6±15.7	NS*	not tested	not tested	-
Cyclosporin A (ng/ml)	not tested	not tested	-	268±37.0	276±85.6	NS*

NS: not significant, Values are mean±standard deviation
* Student's T-test, Hb (hemoglobin; normal 12 g/dl for male), Wbc (white blood cell; normal>5000/mm^3, BUN (blood urea nitrogen; normal<12 mg/dl), Cr (creatinine; normal<1.2 mg/dl), TB (total bilirubin; normal<1.2 mg/dl), Alb (albumin; normal<3.8 g/dl), AST (aspartate aminotransferase; normal<36 IU/L), ALT (alanine aminotransferase; normal<33 IU/L), γ-GT (gamma glutamyl transpeptidase; normal<60 IU/L for male), AP (alkaline phosphatase; normal<250 IU/L), PT (prothrombin time; normal=100%), TC (total cholesterol; normal<250 mg/dl), TG (triglyceride; normal<160 mg/dl), α-FP (alpha-fetoprotein; normal<20 ng/ml).

at post-OLT 5 months.

DISCUSSION

Although many scientific advances have allowed us to choose OLT as the best method to treat end-stage liver diseases, it is still very important to improve long-term survival rate. One of the factors related to better survival after transplantation may be the optimal timing of OLT. Reportedly, the recipient factors affecting transplant outcome are severity of illness, nature of disease, co-existent diseases, and compliance (16). These suggest that OLT should be done earlier during the course of cirrhosis rather than its later stage.

In the present study, performance status of the patients and residual hepatic function among factors selected during peri-OLT period were most important. So, the better performance and/or residual hepatic function, the better is the survival. These support strongly the previous observation.

Serum BUN and total bilirubin levels in the first transplant week were also important predictors of prognosis. Patients who died in the first 2 months had significantly higher serum level of BUN and total bilirubin than survivors over than 1 year. Therefore, it is very important to follow BUN and total bilirubin closely during post-OLT 1 week (over 50 mg/dl in BUN and over 5 mg/dl in total bilirubin) and resolve the problems causing such abnormalities earlier. In the early post-OLT period, the mechanisms of elevation of BUN are volume depletion, cyclosporin A toxicity, or allograft rejection. Although the correction of fluid balance and dose of cyclosporin A are possible, the early confirm of graft dysfunction is not easy because of many factors including reperfusion injury, hepatic artery thrombosis, bile leakage, acute rejection (16). The correctable causes must be defined and managed. Bilirubin level early after surgery is influenced by the preoperative level and by the amount of transfusion required intraoperatively. By the the fourth and fifth day, bilirubin will gradually begin to fall; a climbing bilirubin beyond this point suggestive allgraft dysfunction or a technical problem with the biliary reconstruction (17). To define the various cause of allgraft dysfunction need many intensive studies such as hepatic arteriogram, percutaneous cholangiogram, liver biopsy. In our study, one case showing high BUN, and bilirubin level was diagnosed as hepatic artery thrombosis.

Although bacterial infection was responsible for nearly 80% of the deaths in the 3rd to 12th week after OLT in the Cambridge King's Hospital study (18), our data showed that both infection and acute renal failure were the most frequent causes of death. These suggest that our situation in OLT may be different from that of other

institutes in Western countries. Possibly, in part, both OLT timing and the supportive care immediately after OLT may not be sufficient enough to save patients' lives in our institute. To overcome these two aspects, it will be necessary to recruit the recipients, patients with cirrhosis, who are maintaining better performance and also better residual hepatic function. As another part causing those problems immediate after OLT, surgical factors should be evaluated, too.

Because no effective therapeutic agents for HBV are available and also chronic hepatitis B is highly reactivated in grafted liver (19-24), it has been considered for HBV-related cirrhosis to be a relative contraindication for OLT. In our experience, a patients with HBeAg in whom HBIG had not been administered properly maintaining HBsAb level over than 100 IU/L during post-OLT period was re-infected with HBV and resulted in a progressive hepatic failure with intractable ascites, while patients who had HBV DNA in serum detectable by PCR during pre-OLT period was not infected with HBV after HBIG protocol was maintained. These suggest that removal of replicating HBV in liver and serum before and/or after OLT is an important part to prevent reinfection of HBV.

From the current analysis to determine whether HBV-related cirrhosis was proper for OLT, it was strongly evidenced that a high dose protocol of HBIG was very effective to prevent re-infection of HBV, even though patients were HBeAg-positive during pre-OLT period. It was a key point to maintain safe post-OLT period that high dose HBIG should be used repeatedly without hesitation to maintain high anti-HBs titer, usually 100 IU/ml, in serum. In the European study including 372 HBsAg positive patients, multivariate analysis of pre-transplant variables predictive of post-transplant recurrence of hepatitis B showed recurrence rate lower in patients receiving long-term high dose HBIG immunoprophylaxis ($P<0.001$), those transplanted for HDV superinfection, and those with fulminant liver failure (25). However, the cost of high dose of HBIG is a significant concern. Development of new, less expensive means of binding HBV, individualized dosing with lower target anti-HBs with time from transplantation, or combination therapy to potentially decrease requirements of HBIG are all potential ways to address this problem.

Therefore, to activate OLT for cirrhsis in Korea, recipients should be recruited earlier during the end-stage of cirrhosis. And to maintain a safer post-OLT period for type-B viral cirrhosis, other new agents to remove HBV effectively from serum and liver of the recipients should be used. A lower cost drug like lamivudine (26) would be helpful in the future.

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