Heart transplantation in patients with liver cirrhosis
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Abstract

Objective: Liver cirrhosis is considered to be a contraindication to heart transplantation. However, the clinical outcome of heart transplantation in patients with liver cirrhosis has not been reported. Here, we sought to evaluate the clinical outcome of heart transplantation in cirrhotic patients.

Methods: Data were collected by retrospective chart review. Patients with liver cirrhosis at the time of transplantation were included.

Results: Between 1987 and 2007, 12 patients with liver cirrhosis underwent heart transplantation at the authors’ hospital. Diagnosis of liver cirrhosis was based on preoperative abdominal sonography in five, autopsy in five, and laparotomy in two patients. Causes of heart failure were dilated cardiomyopathy in four, coronary artery disease in three, congenital heart disease in three and valvular heart disease in two patients. Causes of liver cirrhosis were alcoholism in two, cardiac in seven, and unknown in three patients. The Child classification was class A in three, class B in five and class C in four patients. Overall, the hospital mortality rate was 50% and major in-hospital complications occurred in nine patients (75%). Patients with non-cardiomyopathy diagnosis, previous sternotomy, and massive ascites had a high hospital mortality rate. The median follow-up duration was 33.5 months. There was no late death. Late post-transplant complications occurred in four patients and there was no event of liver dysfunction. All survivors were in Child class A at outpatient follow-up.

Conclusions: Although there was high mortality and morbidity, patients with end-stage heart failure and liver cirrhosis can be considered for heart transplantation with careful case selection.

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Keywords: Heart transplantation; Liver cirrhosis; Outcome

1. Introduction

Liver cirrhosis is considered to be a relative or even absolute contraindication to heart transplantation [1]. With the recent advent of medical treatment, patients with liver cirrhosis are now living longer and dying from illnesses other than liver disease [2,3]. Although poor survival might be expected with heart transplantation in patients with liver cirrhosis, the clinical outcome of heart transplantation in cirrhotic patients has never been reported in the literature. Here, we sought to evaluate the clinical outcome of heart transplantation in patients with liver cirrhosis.

2. Patients and methods

2.1. Patients

A total of 311 consecutive patients underwent heart transplantation from July 1987 to May 2007 at the National Taiwan University Hospital. Patients with liver cirrhosis at the time of heart transplantation were included in this study.

2.2. Definition

The diagnosis of liver cirrhosis was based on findings of preoperative abdominal sonography, pathological findings at autopsy, and operative findings at laparotomy. The ultrasonic findings of liver cirrhosis were characterized by a coarsened heterogeneous echo pattern, increased parenchymal echogenicity, and nodularity of the liver surface [4–6]. The pathological features of liver cirrhosis were extensive fibrosis and the formation of regenerative nodules. The operative findings of liver cirrhosis at laparotomy were a contracted liver and gross nodularity of liver surface.

Data on age, sex, diagnosis of heart disease, allograft ischemic time, cardiopulmonary bypass time, renal and liver function tests before and after transplantation, and clinical outcomes were recorded.

2.3. Heart transplantation

All of the procedures of heart transplantation were performed through a median sternotomy. The techniques of cardiopulmonary bypass were described previously [7]. The
operative techniques of heart transplantation in patients with prior cardiac operation were similar to that described previously [8,9]. Postoperative management in intensive care unit was the same as that in routine patients receiving cardiac surgery. Blood components were given whenever needed and no aprotinin was used in our patients. Major postoperative complications were neurological (consciousness disturbance, seizure or stroke), pulmonary (prolonged ventilator support for more than 48 h), infectious (wound infection, bacteremia, pneumonia, or urinary tract infection), gastrointestinal, renal (acute renal failure or need of new dialysis), bleeding (profuse chest tube drainage in need of reoperation), and hepatic decompensation (hepatic function deterioration or hepatic failure).

2.4. Immunosuppression

All patients received triple-drug immunosuppressive therapy according to our heart transplantation protocol previously described [8,9]. We used rabbit antithymocyte globulins for induction therapy. Azathioprine (4 mg/kg) was given 1 h before the operation. Solu-Medrol (1000 mg) was infused while the aortic cross-clamp was released. Rabbit antithymocyte globulin (1.5—2.5 mg/kg/day) was given after transplantation for 5 days. Cyclosporine was started orally within 5 days of transplantation or after the recovery of renal function. Cyclosporine dose was adjusted according to renal function and serum cyclosporine level, which was maintained at the trough level of 300—500 ng/ml during the first three months after transplantation and 200—300 ng/ml one year after transplantation. Azathiopine was given at 1—2 mg/kg/day after transplantation, with the dose adjusted to maintain a white blood cell count 4000—6000/mm². Prednisone (0.5 mg/kg/day) was started on the second postoperative day and tapered to 0.2 mg/kg/day by the first month after transplantation. Tacrolimus and mycophenolate mofetil were used for recurrent rejection or severe adverse reactions to cyclosporine and azathioprine. Since 2004, we started to use mycophenolate mofetil for primary immunosuppression instead of azathioprine. To prevent nephrotoxicity, cyclosporine dose was decreased to maintain serum trough level of 250—350 ng/ml during the first three months after transplantation and 150—250 ng/ml one year after transplantation.

All patients were followed monthly at special cardiac transplantation clinic. Standard chest roentgenogram, blood tests, electrocardiogram and physical examinations were routinely performed at regular intervals.

3. Results

From 1997 to 2007, a total of 12 patients undergoing heart transplantation had liver cirrhosis. The diagnosis of liver cirrhosis was based on preoperative abdominal sonography in five patients, based on autopsy in five patients and based on laparotomy in two patients.

3.1. Abdominal sonography

Abdominal sonography was performed in all 311 patients and liver cirrhosis was found in five patients (2%). Of the five cirrhotic patients diagnosed by abdominal sonography, there were four men and one woman with a median age of 45 years (range 32—53 years). The causes of heart failure were dilated cardiomyopathy in three patients, and valvular heart disease, and coronary artery disease each in one patient. Patient demographics and laboratory data at the time of transplantation were listed in Table 1. No patient had a previous sternotomy. Two patients had a high level of serum total bilirubin. One patient had a high serum creatinine and required continuous dialysis therapy before transplantation. No patient had the prothrombin time international ratio over 1.5. The cause of liver cirrhosis was alcoholism in two patients, cardiac in two patients and not specified in one patient. None of our patients had positive hepatitis B virus surface antigenemia or antibody against hepatitis C virus. Before transplantation, only one patient received percutaneous liver biopsy, which showed cardiac cirrhosis. All patients underwent orthotopic heart transplantation. The median durations of allograft ischemic time and cardiopulmonary bypass were 221 min (range, 95—250) and 123 min (range, 72—165). The Child classification at the time of
transplantation was class A in two patients, class B in two
patients and class C in one patient.

Data of operation and clinical outcome were listed in
Table 2. There was no hospital mortality. Major post-
operative complications occurred in three patients with
severe right heart failure requiring extracorporeal mem-
brane oxygenation, profuse postoperative bleeding requir-
ing reoperation and methicillin-resistant *Staphylococcus
aureus* bacteremia, and large pericardial effusion each in
one patient.

3.2. Autopsy

Of the five cirrhotic patients diagnosed by autopsy,
pathological examination of the livers showed pictures of
cardiac cirrhosis with centrilobular necrosis and varying
degree of fibrosis (Table 1). The findings of preoperative
abdominal sonography were liver congestion and massive
ascites in four patients, and only liver congestion in one
patient. None of them were diagnosed as liver cirrhosis by
abdominal sonography. All patients had previous sternotomy
because of underlying heart disease (Table 1). Two patients
having complex congenital heart disease, single ventricle
physiology and failed previous cardiac operations (one total
cavopulmonary connection and one Fontan) died of surgical
bleeding shortly after transplantation. One 39-year-old
female having pulmonary atresia and previous Rastelli
operation also died of surgical bleeding after transplanta-
tion. One 36-year-old female having rheumatic heart disease
post aortic and mitral valve replacement died of sepsis and
severe gastrointestinal bleeding. Autopsy showed gang-
renous changes of gastrointestinal tracts because of
disseminated intravascular coagulation. One 60-year-old
female having severe coronary artery disease underwent
orthotopic heart transplantation because of small vessel
disease and severe right heart failure. The postoperative
course was complicated with right heart failure requiring
temporary support with extracorporeal membrane oxygena-
tion. She died of nosocomial pneumonia and sepsis caused by
methicillin-resistant *S. aureus*.

3.3. Laparotomy

Two patients were diagnosed to have liver cirrhosis by
laparotomy (Tables 1 and 2). The preoperative ultrasound
findings were liver congestion and heterogeneous echogeni-
city of liver parenchyma. One 46-year-old male having
dilated cardiomyopathy underwent partial left ventriculect-
omy because of refractory heart failure. Heart failure
recurred 6 months later. And he underwent successful
orthotopic heart transplantation at 11 months after previous
ventriculectomy. At sternotomy, the abdomen was incident-
tally entered and micronodular liver cirrhosis was found. One
44-year-old male having severe coronary artery disease
underwent orthotopic heart transplantation because of small
vessel disease and severe biventricular failure. The post-
operative course was complicated with primary graft failure
requiring temporary support with extracorporeal membrane
oxygenation and ischemic bowel disease. Severe liver
cirrhosis was found at laparotomy. He died of severe sepsis
and liver failure.

Overall, the hospital mortality rate was 50% and major in-
hospital complications occurred in nine patients (75%). The
hospital mortality rate was higher in patients with non-
cardiomyopathy diagnosis (6/8 vs 0/4), previous sternotomy
(5/6 vs 1/6), and massive ascites (5/6 vs 1/6), but not
advanced Child class.

3.4. Late outcome

Of the six patients who survived at discharge, there was no
late death (Table 2). The median follow-up duration was 33.5
months (range, 8—104). Late post-transplant complications
occurred in four patients. One patient developed chronic renal
failure and received regular hemodialysis at 27 months after
transplantation. One patient had laryngeal carcinoma at 30
months after transplantation. One patient had late cardiac
allograft failure and chronic renal insufficiency. He underwent
redo heart and kidney transplantation at 73 months after
transplantation. As shown in Table 3, all patients were in Child
class A at the time of last outpatient follow-up.
It was reported that cirrhosis undergo transplantation. It was reported that with end-stage heart failure and clinically silent cardiac contraindication to heart transplantation, some patients cirrhosis is considered to be a relative or even absolute and albumin are within the normal range. Although liver cardiac cirrhosis, serum levels of liver enzymes, bilirubin, and three forms of clinical presentation have been reported: prolonged right ventricular milder alteration of liver function tests, ischemic hepatitis, and cardiac cirrhosis [13,14]. Prolonged right ventricular cardiomyopathy, but overt heart failure is not observed in two patients, cardiac in seven patients, and unknown in three patients. None of our patients had cirrhosis caused by hepatitis virus infection. Two cases of alcoholic liver cirrhosis underwent heart transplantation because of dilated cardiomyopathy. All seven patients with cardiac cirrhosis had a prolonged course of severe right heart failure. Preoperative abdominal sonography failed to disclose liver cirrhosis in 7 of 12 patients. Abdominal sonography will underestimate the incidence of liver cirrhosis in heart transplant recipients. The observed hepatic dysfunction might be related to both the congestion from heart failure and the primary liver disease.

4. Discussion

Evaluation of heart transplant candidates includes a careful analysis of medical comorbid conditions that may negatively affect outcome after transplantation. Any coexistent systemic illness that limits survival independent of heart disease should be considered a possible contraindication to heart transplantation [1]. It is recommended that patients with abnormal liver function should not be listed for heart transplantation until liver cirrhosis has been excluded [1]. However, the measured hepatic dysfunction might be related to both the congestion from heart failure and the primary liver disease.

4.1. Heart failure in cirrhosis

Liver cirrhosis is associated with a wide range of cardiovascular abnormalities, which are usually characterized by an increased cardiac output and a decreased peripheral arterial resistance [10–12]. Some patients with alcoholic liver cirrhosis might have a subclinical cardiomyopathy with evidence of abnormal ventricular function induced by stress. However, obvious congestive alcoholic cardiomyopathy develops only in a small percentage of cirrhotic patients, but the concurrent presence of cirrhosis seems to retard the occurrence of overt heart failure. Even nonalcoholic liver cirrhosis may be associated with latent cardiomyopathy, but overt heart failure is not observed [11,12].

In contrast to that, heart diseases might affect the liver and three forms of clinical presentation have been reported: mild alterations of liver function test, ischemic hepatitis, and cardiac cirrhosis [13,14]. Prolonged right ventricular failure and systemic venous hypertension will lead to cardiac cirrhosis. Cardiac cirrhosis is a clinically silent disorder and laboratory tests have only a small role in the diagnosis of cardiac cirrhosis [13,14]. In the majority of patients with cardiac cirrhosis, serum levels of liver enzymes, bilirubin, and albumin are within the normal range. Although liver cirrhosis is considered to be a relative or even absolute contraindication to heart transplantation, some patients with end-stage heart failure and clinically silent cardiac cirrhosis undergo transplantation. It was reported that cardiac cirrhosis was found at autopsy in 75% of the early deaths of heart-lung transplant recipients with right ventricular failure and hyperbilirubinemia [15]. In this current series, the causes of liver cirrhosis were alcoholism in two patients, cardiac in seven patients, and unknown in three patients. None of our patients had cirrhosis caused by hepatitis virus infection. Two cases of alcoholic liver cirrhosis underwent heart transplantation because of dilated cardiomyopathy. All seven patients with cardiac cirrhosis had a prolonged course of severe right heart failure. Preoperative abdominal sonography failed to disclose liver cirrhosis in 7 of 12 patients. Abdominal sonography will underestimate the incidence of liver cirrhosis in heart transplant recipients.

4.2. Cardiac surgery in cirrhosis

The clinical outcome of cardiac surgery in patients with liver cirrhosis was reported infrequently [7,16–19]. Patients with mild liver cirrhosis can well tolerate cardiac surgical procedures. Advanced liver cirrhosis (Child class B and C or Child score ≥ 8) was thought as an absolute contraindication to cardiac surgery with the use of cardiopulmonary bypass [16–19]. Major postoperative complications will develop in more than 80% of patients with advanced liver cirrhosis, and the in-hospital mortality rate will be up to 50–100% [16–19]. However, the results are still controversial [7].

The clinical outcome of heart transplantation in patients with liver cirrhosis has never been reported in the literature. In this current small series of 12 patients, the Child classification at the time of transplantation was class A in 3 patients, class B in 5 patients and class C in 4 patients. Although the hospital mortality and postoperative complications were common in cirrhotic patients undergoing heart transplantation, the mortality rate was low and the late outcome was acceptable in those patients with a diagnosis of dilated cardiomyopathy, no ascites and no previous sternotomy.

4.3. Late outcome

The late outcome of heart transplantation in patients with liver cirrhosis and end-stage heart failure is still unknown. Combined heart and liver transplantation have been

Table 3 Before and after of Child score and Child class of heart transplantation in patients who survived at discharge

<table>
<thead>
<tr>
<th>No.</th>
<th>Time</th>
<th>Albumin (g/dl)</th>
<th>Total bilirubin (mg/dl)</th>
<th>Encephalopathy</th>
<th>Ascites</th>
<th>Prolonged PT (s)</th>
<th>Child score</th>
<th>Child class</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Before</td>
<td>3.4</td>
<td>1.5</td>
<td>None</td>
<td>Moderate</td>
<td>4—6</td>
<td>8</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>4.8</td>
<td>1.14</td>
<td>None</td>
<td>Absent</td>
<td>0—4</td>
<td>5</td>
<td>A</td>
</tr>
<tr>
<td>2</td>
<td>Before</td>
<td>4.3</td>
<td>0.9</td>
<td>None</td>
<td>Absent</td>
<td>0—4</td>
<td>5</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>4.9</td>
<td>1.27</td>
<td>None</td>
<td>Absent</td>
<td>0—4</td>
<td>5</td>
<td>A</td>
</tr>
<tr>
<td>3</td>
<td>Before</td>
<td>3.7</td>
<td>3.02</td>
<td>None</td>
<td>Refractory</td>
<td>4—6</td>
<td>10</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>4.5</td>
<td>1.5</td>
<td>None</td>
<td>Moderate</td>
<td>0—4</td>
<td>6</td>
<td>A</td>
</tr>
<tr>
<td>4</td>
<td>Before</td>
<td>4.02</td>
<td>3.8</td>
<td>None</td>
<td>Absent</td>
<td>0—4</td>
<td>7</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>4.55</td>
<td>1.19</td>
<td>None</td>
<td>Absent</td>
<td>0—4</td>
<td>5</td>
<td>A</td>
</tr>
<tr>
<td>5</td>
<td>Before</td>
<td>4.55</td>
<td>1.27</td>
<td>None</td>
<td>Absent</td>
<td>0—4</td>
<td>5</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>4.7</td>
<td>1.0</td>
<td>None</td>
<td>Absent</td>
<td>0—4</td>
<td>5</td>
<td>A</td>
</tr>
<tr>
<td>11</td>
<td>Before</td>
<td>2.9</td>
<td>3.1</td>
<td>None</td>
<td>Absent</td>
<td>≥6</td>
<td>11</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>4.5</td>
<td>0.82</td>
<td>None</td>
<td>Absent</td>
<td>0—4</td>
<td>5</td>
<td>A</td>
</tr>
</tbody>
</table>

PT: prothrombin time.
performed in patients with end-stage heart failure and liver cirrhosis, which were usually caused by some inherited disorders [20–21]. It was reported that 80% and 70% of patients survived at 1 and 3 years after combined heart and liver transplantation [20]. In this current series, there was no late death with a median follow-up duration of 33.5 months. All patients who survived at discharge were in Child class A at last outpatient follow-up.

Severe heart failure may aggravate clinical condition of cirrhotic patients and hepatic decompensation could develop after aggravated heart failure in patients with mild liver cirrhosis. Once the heart failure was surgically corrected, the exacerbated liver function will return to its baseline. Therefore, an improved clinical outcome could be achieved even in those patients with clinically severe liver failure before heart transplantation. With a critical donor shortage worldwide, isolated heart transplantation provided an alternative to combined heart and liver transplantation in patients with end-stage heart failure and liver cirrhosis.

4.4. Regression of cirrhosis

Once established, liver cirrhosis has generally been considered to be irreversible. The diagnosis of liver cirrhosis was made clinically on the basis of signs of end-stage liver disease, such as ascites, hyperbilirubinemia, hypoalbuminemia, coagulopathy and encephalopathy. These features continue to indicate a poor prognosis in the absence of liver transplantation and are still used to classify the severity of liver disease. However, Child classification may be unreliable in heart transplant recipients because some of them may have warfarin therapy or severe cardiac cachexia leading to a prolonged prothrombin time and hypoalbuminemia. Cirrhosis is now frequently diagnosed at an early stage by percutaneous liver biopsy and abdominal sonography. But the current staging methods do not discriminate sufficiently between different degrees of cirrhosis [22–24].

Recently the idea that liver cirrhosis is reversible is taking root. Liver fibrosis can regress when the initial disease is controlled or cured. Advances in the treatment of liver diseases have made it increasingly apparent that medical treatment may be beneficial even for patients with advanced cirrhosis. Furthermore, in some cases fibrosis and even frank cirrhosis have appeared to regress with treatment [22–24]. Liver cirrhosis should no longer be considered as contra-indication for heart transplantation.

4.5. Study limitation

This study was limited by small case numbers, it being a retrospective study, a lack of preoperative liver biopsy in every case and a short duration of follow-up. Seven of our 12 patients were identified by gross inspection or postmortem examination, but those patients who might have cirrhosis and did not die or have laparotomy were unable to be detected. The true operative mortality rate of heart transplantation in patients with liver cirrhosis and its risk factors for death remain unknown.

Although the results were preliminary, this study is one of the largest series of heart transplantation in patients with liver cirrhosis. Heart transplant candidates should be carefully selected for the presence of liver cirrhosis, especially in patients with severe right ventricular failure, ascites and previous history of alcoholism. Liver biopsy remains a pivotal role in evaluation of the grade of inflammation and stage of cirrhosis before transplantation. Liver biopsy may be indicated in patients with cardiac ascites and hypoalbuminemia before transplantation [25]. The presence of extensive liver fibrosis would disqualify patients from transplantation and the only viable option for these patients with cardiac cirrhosis would be combined heart and liver transplantation.

Heart transplantation is limited by the scarcity of donor organs and stringent selection criteria for both donors and recipients. Clinical success has led to the development of an alternate list strategy, matching marginal cardiac allografts with recipients who do not meet standard criteria for heart transplantation. Liver cirrhosis remains a relative contraindication to heart transplantation. Because of an uncertain long-term outcome, patients with liver cirrhosis could be put on the alternate list for heart transplantation especially for those patients with cardiomyopathy in diagnosis, no previous sternotomy, and no massive ascites.

4.6. Conclusions

Although there was high mortality and morbidity, patients with end-stage heart failure and liver cirrhosis can be considered for heart transplantation with careful case selection.

References


