

Combined Heart and Liver Transplantation: The Asan Medical Center Experience

Hyo-In Choi, M.D.¹, Tae-Jin Yun, M.D.², Sung-Ho Jung, M.D.², Jae Won Lee, M.D.²,
Gi-Won Song, M.D.³, Sung-Gyu Lee, M.D.³, Kyung Mo Kim, M.D.⁴ and Jae-Joong Kim, M.D.¹

Division of Cardiology, Department of Internal Medicine¹, Department of Thoracic and Cardiovascular Surgery²,
Division of Liver Transplantation and Hepato-Biliary Surgery, Department of Surgery³, Department of Pediatrics⁴,
Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Combined heart-liver transplantation (CHLT) is an increasingly accepted treatment for select patients with advanced heart and liver disease. However, CHLT are infrequently performed, despite growing optimism about their effectiveness. Here, we report Asan Medical Center experience with CHLT in three patients presenting with advanced heart and liver failure. One patient died of brain swelling because of intractable hyperammonemia on postoperative day 9. The two other patients were still alive at 53 and 9 months postsurgery. None of these patients required readmission for cardiac or hepatic graft dysfunction and no rejection episodes were detected on routine cardiac biopsies. This is the first report of CHLT cases from Korea.

Key Words: Heart transplantation, Liver transplantation, Multi-organ transplant, End-stage heart disease

중심 단어: 심장이식, 간이식, 다장기이식, 말기 심부전

INTRODUCTION

Patients presenting with concomitant end-stage liver and heart disease represent a significant clinical challenge. This extremely morbid cohort requires intensive management and intervention to prevent death. However, intervention itself is associated with high risks. The first combined heart-liver transplantation (CHLT) was performed in a pediatric patient with familial hypercholesterolemia and heart failure secondary to coronary artery disease(1). Initially performed for patients with familial hypercholesterolemia, the indications for CHLT have since been expanded in light of

early reports of satisfactory survival outcomes. CHLT is now performed for a variety of illnesses that result in dual vital organ failure (hemochromatosis, familial hypercholesterolemia, and amyloidosis) as well as for patients with end-stage liver failure or heart failure who are considered unfit for isolated transplantation because of severe cardiac or liver disease(2-6). In the 30 years since it was first performed, the increasing frequency of CHLT procedures reflects growing optimism that patients who were traditionally deemed unacceptable candidates for heart transplant alone because of concurrent liver dysfunction can now be treated(7). The paradigm shift to considering more patients for dual organ transplantation affords hope to patients who otherwise have few therapeutic options.

Although the indications for CHLT have increased, it is still rarely performed in Korea due to the difficulty and complexity of the required surgical techniques. As acceptance of CHLT grows, it becomes increasingly important to share clinical experiences. The currently available data have confirmed that CHLT produces acceptable outcomes for se-

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Corresponding author: Jae-Joong Kim

Division of Cardiology, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea
Tel: 82-2-3010-3154, Fax: 82-2-486-5918
E-mail: jjkim@amc.seoul.kr

lected patients with heart and liver dysfunction when performed by experienced heart and liver transplant teams. We here report our single-center experience with CHLT performed for various cases in order to disseminate further useful information on the clinical course and management associated with this surgery and help to guide future CHLT procedures in Korea and elsewhere.

CASE REPORTS

Main preoperative parameters for the three patients are listed in Table 1.

1. Case 1

A 14-year-old girl who had experienced jaundice for one week was transferred to our center with a preliminary diagnosis of fulminant Wilson disease, a diagnosis later confirmed by the identification of an ATP7B mutation (homozygote c.2333G>T). On admission, her serum ceruloplasmin concentration was low (8.7 mg/dL) and her 24-hour urinary copper output was high (4,504 µg/day). She was negative for hepatitis viruses A, B, and C; cytomegalovirus; Epstein-Barr virus; and autoimmune hepatitis. Echocardiography

results were normal with a left ventricular ejection fraction (LVEF) of 70%. Treatment with trientine and zinc was initiated immediately. Although a liver transplant was recommended, her parents wanted her to be treated medically. She was started on regular exchange transfusion and plasmapheresis, resulting in an improvement in hemolytic parameters after 5 months, but with no improvement in her liver dysfunction. Although a liver transplantation was again recommended, her parents again refused consent. Due to hemolytic anemia, she was given frequent red blood cell transfusions to maintain her hemoglobin concentration above 6 g/dL.

Two weeks prior to transplantation, she experienced an episode of primary bacterial peritonitis, which was improved by treatment with antibiotics. An echocardiogram showed good ventricular function (LVEF 55%). Eight days before her transplantation, she developed hepatorenal syndrome, necessitating continuous renal replacement therapy (CRRT). One day later, a mental change occurred, along with evidence of heart failure, with an echocardiogram showing an LVEF of 30%. At 5 days before transplantation, her heart failure became aggravated, with an LVEF of 17%. An electrocardiogram (ECG) showed no evidence of myocardial is-

Table 1. Main preoperative parameters of the three combined heart and liver recipients

Parameter	Case 1	Case 2	Case 3
Age (yr)	14	45	46
Sex	Female	Male	Male
BMI (kg/m ²)	21.7	19.4	21.8
Indication for HT	CHF	CHF	HCMP
Indication for LT	Wilson disease	Hepatitis B cirrhosis	Ischemic hepatopathy combined with toxic hepatitis
Creatinine (mg/dL)	0.6	2.1	1.0
Hemodialysis	Yes	Yes	Yes
PT (INR)	3.8	2.0	1.5
Total bilirubin (mg/dL)	22.1	24.9	24.0
AST (IU/L)	1,449	125	23
ALT (IU/L)	312	49	19
MELD at transplant	40	40	37
ECMO support at registration	Yes	Yes	No
Ventilator support at registration	Yes	Yes	Yes
Inotropic support at registration	Yes	Yes	Yes

Abbreviations: BMI, body mass index; HT, heart transplantation; CHF, congestive heart failure; HCMP, hypertrophic cardiomyopathy; LT, liver transplantation; PT, prothrombin time; INR, international normalized ratio; AST, aspartate aminotransferase; ALT, alanine transaminase; MELD, model for end-stage liver disease; ECMO, extracorporeal membrane oxygenation.

chemia or arrhythmia. Since there was no evidence of infection or sepsis, the cause of severe myocardial dysfunction was unknown. Her blood pressure decreased to 70/40 mmHg, and venoarterial (VA) extracorporeal membrane oxygenation (ECMO) was started using the right internal jugular and left femoral veins to right femoral artery circulation, but without improvement in heart functions. Application of a molecular adsorbents recirculation system (MARS) for liver support did not improve the patient's consciousness. Because this patient showed no improvement in heart or liver function after 5 days of maximal ventilatory support, VA ECMO, MARS, and CRRT, we planned a simultaneous CHLT.

The diagnosis of liver failure due to Wilson disease and severe heart failure of unknown origin enabled this patient to be listed for dual organ transplant on the Korean Network for Organ Sharing (KONOS), with a cardiac status of 0 and a model for end-stage liver disease (MELD) score of 40. Liver and heart donor grafts were available from a deceased 46-year-old male, who was ABO compatible and became brain dead due to an acute subdural hemorrhage. CHLT was performed in June 2007, using the technique described previously(8). Briefly, after median sternotomy and pericardiotomy, the aortic, superior, and inferior vena cava were cannulated and connected to the left femoral venous cannula through a cardiopulmonary bypass (CPB) circuit. During CPB, a cardiectomy was performed and the donor heart implanted using standard methods. For liver transplantation, the inferior vena cava and portal vein anastomoses were performed under CPB, with hepatic artery and bile duct anastomoses performed after weaning from CPB. At that time, her blood pressure was 80/50 mmHg, her central venous pressure (CVP) was 20 mmHg, and her cardiac and hepatic ischemic times were 242 and 360 minutes, respectively. She was started on immunosuppression with methylprednisolone, basiliximab, and mycophenolate mofetil. The explanted liver showed diffuse macronodular cirrhosis with massive hepatic necrosis. The explanted heart showed myocardial hypertrophy, multifocal myocardial degeneration, and hemosiderosis, indicative of Wilson disease or iron overload.

On postoperative day (POD) 1, the patient developed *Acinetobacter baumannii* sepsis and her CVP increased to

28 mmHg with no detectable cause. An echocardiogram on POD 2 showed good ventricular function (LVEF 88%) and grade 1 tricuspid regurgitation (TR) with TR velocity of 2.4 m/sec. The next day, her graft liver function had recovered, with a prothrombin time of 58.4% (1.30 international normalized ratio); total and direct bilirubin concentrations of 11.1 and 6.4 mg/dL, respectively; and aspartate aminotransferase and alanine transaminase concentrations of 98 and 126 IU/L, respectively. In addition, her CVP had decreased to 16 mmHg. Abdominal computed tomography (CT) showed no active bleeding or hematoma. Brain CT revealed a small acute subdural hemorrhage. She showed slight recovery in consciousness, with some responses on verbal order and pain. This was followed by an abrupt worsening of consciousness and seizures, with an increase in her ammonia concentration to 2,467 μ mol/L and a CVP increase to 30 mmHg with no response to medical therapy. Despite intensive medical treatment with sodium benzoate, sodium phenylbutyrate, L-arginine, and CRRT, as well as two sessions of MARS, her hyperammonemia could not be controlled, perhaps due to a glutamine synthetase deficiency. Serum amino acid analysis excluded specific metabolic disorders such as ornithine transcarbamylase deficiency and citrullinemia. On POD 9, the patient died of brain swelling due to intractable hyperammonemia.

2. Case 2

A 45-year-old male diagnosed with end-stage liver disease due to chronic hepatitis B was admitted to Asan Medical Center with hepatic encephalopathy. The patient's history was notable for recurrent spontaneous bacterial peritonitis (four episodes during last 6 months, two episodes associated with septic shock). Three months prior to this admission, a transthoracic echocardiography, which was performed as part of the pre-transplant workup, had revealed a normal biventricular function with a LVEF of 64%. However, echocardiography done at this time revealed marked global hypokinesia of the left ventricular with a reduction of ejection fraction to about 17%. No evidence of myocardial ischemia or myocarditis was detected by ECG, cardiac enzymes, or echocardiography. His multiorgan failure rapidly progressed to include acute kidney injury, and 7 days before transplantation, he required CRRT. Despite

multiple high-dose inotropes, a severe hemodynamic instability in this patient required VA ECMO support 2 days before transplantation. His MELD score was 40 at the time of transplantation. Fulminant hepatic failure and refractory cardiogenic shock were the indications for CHLT.

The CHLT procedure was performed on September 2012 and began with orthotopic cardiac transplantation using the bicaval anastomosis technique. After performing a thoracotomy and commencing a CPB through cannulation of the superior and inferior vena cava and ascending aorta, the recipient's heart was removed and replaced with a graft from a 41-year-old male who was ABO compatible and had suffered brain death due to a traumatic intracerebral hemorrhage. Satisfactory hemodynamic parameters were maintained throughout the procedure with minimal inotropic support (isoproterenol, 0.05 µg/kg/min). The abdomen was entered through an inverted T incision. Liver transplantation was performed orthotopically using the conventional caval reconstruction technique with venovenous bypass. Portal and arterial reperfusion were sequentially obtained thereafter. The total ischemia time was 76 minutes for the heart and 305 minutes for the liver. Immunosuppression included induction with 20 mg of baxiliximab at day 0, continuous intravenous tacrolimus to reach blood levels of 6 to 8 ng/mL and tapered doses of steroids. Mycophenolate mofetil was given from POD 2. The macroscopic and histologic examination of the explanted liver confirmed the diagnosis of hepatitis B associated cirrhosis. The pathology of explanted heart showed mild but extensive myocardial atrophy and moderate atherosclerosis of the left circumflex and right coronary artery.

Postoperatively, the cardiocirculatory performance of this patient remained satisfactory, and inotropic drugs were definitively stopped on POD 3. An echocardiogram on POD 12 showed a LVEF of 65%, normal right ventricle size and function with mild TR, and no pericardial effusion. The estimated pulmonary artery pressure from the TR jet velocity was 45 to 50 mmHg. Serial Doppler ultrasonography of the liver showed sustained good graft perfusion with patent portosystemic veins and laboratory markers of hepatic function rapidly normalized after transplantation. Myocardial biopsy performed on POD 45 did not show evidence of acute cellular rejection. Renal function gradually improved and he-

modialysis was discontinued on POD 36. However, weaning phase from the ventilator complicated the postoperative course. In addition to bilateral pleural effusion and bilateral pneumothorax, the patient presented with respiratory muscle fatigue. Weaning trials were not tolerated and immediately led to dyspnea, tachypnea, and agitation. The patient underwent daily T-piece trials and pressure support could be decreased daily. On POD 52, the tracheostomy was eventually removed uneventfully.

The patient's liver chemistry test results have since remained normal and he is New York Heart Association class 1. Mild renal insufficiency persists with a serum creatinine of 1.7 mg/dL. During 58 months of follow-up, there have been no acute rejection episodes and routine surveillance coronary angiography has revealed no allograft vasculopathy. Immunosuppression includes tacrolimus, mycophenolate mofetil, and methylprednisolone. He has returned to work with no acute or chronic allograft rejection at 4 years post-transplant.

3. Case 3

A 46-year-old male diagnosed with burn-out phase of hypertrophic cardiomyopathy and toxic hepatitis underwent CHLT at our center in July 2016. He initially presented in 2009 with shortness of breath, orthopnea, and peripheral pitting edema and was diagnosed with burn-out phase of hypertrophic cardiomyopathy (LVEF of 37%). He also had diabetes, chronic kidney disease (CKD), atrial fibrillation and hypothyroidism. Since then, he had recurrent hospitalizations due to decompensated heart failure. One month before admission, he consumed a traditional herbal medication containing extract of oyster mushroom to improve renal function. Ten days later, he was admitted to another hospital due to decompensated heart failure. In addition to decompensated heart failure, a diagnosis of toxic hepatitis was made based on his clinical history, the findings for viral markers and other laboratory data. Despite receiving optimal treatment for heart failure, he continued to deteriorate and was eventually referred to Asan Medical Center for CHLT. He developed hepatic encephalopathy and required CRRT due to acute kidney injury following cardiogenic shock. Before transplantation, his MELD score was 37 and an echocardiography revealed a diffuse thickened right and

left ventricle, and decreased biventricular systolic function (LVEF of 33%). He was eventually placed on a mechanical ventilator as a result of intractable pulmonary edema and was dependent on a high dose of inotropes and vasoconstrictors to maintain his hemodynamics. Indication for CHLT was severe ischemic hepatopathy combined with toxic hepatitis in the setting of end-stage heart failure. Combined heart-liver-kidney transplantation was not considered an option because, although he had CKD, there was the possibility of renal function recovery.

The patient underwent CHLT with operative management similar to patient 2 (case 2). After performing a thoracotomy and starting CPB through cannulation of the superior and inferior vena cava and ascending aorta, the recipient's heart was removed and replaced with the graft from an 18-year-old male who died from asphyxia. The liver transplant was completed and the abdomen was closed with the patient on stable doses of dobutamine (3 µg/kg/min). The total ischemic time was 101 minutes for the heart and 309 minutes for the liver. The explanted liver showed severe cholangiolar and canalicular cholestasis, periportal fibrosis without hepatic necrosis, indicative of ischemic hepatopathy combined with toxic hepatitis. Histologic features of explanted heart were consistent with burn-out phase of hypertrophic cardiomyopathy (hypertrophy of cardiac myocytes, intermyofibrillar fibrosis, and patchy epicardial lymphocytic infiltration). Myocyte disarray was not seen in this case.

Immediate postoperative echocardiography identified a large pericardial hematoma compressing the right sided cardiac chambers. His clinical course was stable until 6 days after surgery, at which time when his hemodynamics deteriorated requiring a reoperation. A large amount of hematoma was evacuated from the pericardial sack, with an immediate improvement in blood pressure and heart rate. Two pigtail catheters were placed in the pericardium to drain any residual hematoma. Echocardiography after evacuation surgery revealed normal biventricular size and function with hematoma in the RV anterior side without any definite hemodynamic significance.

On POD 12, the patient complained of right upper quadrant abdominal pain and severe hematochezia. Total colonoscopy revealed longitudinal ulcerations, mucosal edema, and active oozing bleeding in the hepatic flexure. Ischemic in-

jury during pre-transplant hypoperfusion caused ischemic colitis and reperfusion resulted in bleeding from the ulcerated portions. Multiple hemoclips were placed at the site of bleeding for hemostasis. Thereafter, a total of seven endoscopic interventions were needed to control for recurrent hematochezia.

A myocardial biopsy performed on POD 38 did not show any evidence of acute cellular rejection. A serial Doppler ultrasonography of the liver indicated sustained good graft perfusion with patent portosystemic veins and laboratory markers of hepatic function were found to have rapidly normalized. In the 9 months after CHLT, the cardiac and hepatic performance in this patient remained excellent with no rejection episodes. He had CKD for 7 years, and he is currently on maintenance hemodialysis.

DISCUSSION

We have summarized the perioperative course of three patients who underwent simultaneous CHLT at Asan Medical Center and confirmed that this procedure has acceptable outcomes for selected patients with advanced heart and liver dysfunction. Our experiences are consistent with the encouraging results reported from other centers(9-12). There were 208 CHLT operations performed in the United States between January 1988 and October 2016(7). The majority of these were performed at high-volume centers. The institutional experiences and reviews of the national experience in the United States using the Organ Procurement and Transplantation Network (OPTN) database suggested that despite the high morbidity and mortality rates associated with multiorgan dysfunction, early and long-term patient survival after CHLT was similar to the survival outcomes after isolated heart or liver transplantation(13).

There have been two large studies of CHLT to date using the United Network for Organ Sharing (UNOS) database. In the first of these studies, Te et al.(14) described the experiences in centers in the United States from October 1987 to December 2005, during which time there were 41 cases of CHLT and six cases of combined heart-liver-kidney transplant recorded. The most common immunosuppressive regimens were corticosteroids and either tacrolimus or cyclosporine. The 1- and 5-year survival rates were 84.8% and

75.6%, respectively. The heart graft survival outcomes at 1- and 5-year were 84.8% and 75.6% and the liver graft survival at 1- and 5-year was 82.4% and 73.5%. The authors concluded that CHLT is a viable option for candidates requiring combined organ transplantation and that the outcomes of this surgery were comparable to those for single-organ recipients(14). Cannon et al.(15) completed their review of the United States experience with CHLT using the UNOS data on 97 cases reported between October 1987 and December 2010. In nine of these patients a simultaneous kidney transplant was performed. In 10 of these cases, a simultaneous lung transplant was performed. Cardiac allograft survival rates at 1-, 5-, and 10-years were similar between CHLT and isolated cardiac transplantation (83.5%, 73.2%, 71.5% vs. 82.6%, 71.9%, 63.2%, $P=0.341$). Liver graft survival at 1-, 5-, and 10-year was found to be similar between CHLT patients and isolated liver patients (83.4%, 72.8%, 71.0% vs. 79.4%, 71%, 65.1%, $P=0.894$). Multivariable analysis that controlled for recipient age, recipient gender, and donor age, found no significant difference between the risk of patient death or graft failure in the CHLT group versus patients who received an isolated liver transplant (hazard ratio [HR], 1.30; 95% confidence interval [CI], 0.93 to 1.84; $P=0.127$) (HR, 1.09; 95% CI, 0.79 to 1.52; $P=0.589$). There was also no significant difference found between CHLT and isolated heart transplant in terms of risk of patient death or graft failure (HR, 0.90; 95% CI, 0.64 to 1.26; $P=0.538$) (HR, 0.86; 95% CI, 0.62 to 1.21; $P=0.386$). These authors concluded that CHLT is a safe procedure with comparable graft survival rates to liver-alone and cardiac-alone transplantations(15).

Despite advances in multiorgan transplantation, CHLT is rarely performed in Korea. Combined liver and thoracic organ transplantation is a more complex procedure and CHLT was performed only in five patients since 2007 to April 2017 in Korea. During the same period, there were 21 cases of combined heart-lung transplantation and 15 cases of combined heart-kidney transplantation recorded(16).

To achieve good results in these extremely sick patients, there are a few considerations worth emphasizing. The first is the decision to perform a combined rather than an isolated transplantation. Current indications for CHLT can be summarized as end stage heart and liver disease, and end

stage heart disease which need liver transplantation to correct an underlying disorder. Familial amyloid polyneuropathy and heart failure with associated cardiac cirrhosis are the most common indications for CHLT(14,15,17,18). Myocardial dysfunction in our three patients was severe enough to suggest an unacceptable risk of heart failure during or after liver transplantation. In all three cases, we regarded the likelihood of reversing heart failure to be very low because heart function had not improved under optimal treatment in any of the patients. These patients have been traditionally deemed to be unacceptable candidates for liver transplant alone because of their concurrent advanced heart failure. CHLT thus was a lifesaving treatment in these cases. Nonetheless, the predominant notion is that donor organs are such a scarce resource that as many patients as possible should be served and, therefore, transplanting multiple organs into 1 recipient should be decided carefully. But the KONOS has made it clear in its rules that patients who are awaiting multiple-organ transplantation should be preferred over patients who are awaiting a single organ. In all of three cases, the heart and the liver were allocated to the patients from the same donor. Another crucial point to make in relation to CHLT is the importance of optimal intensive postoperative management. The very different outcomes between case 1 and cases 2 and 3 in our current study were mainly due to their very different postoperative conditions. Although patient 1 (case 1) maintained good cardiac function and normal CVP immediately after transplant, she developed sepsis with aggravated coagulopathy, requiring high doses of inotropic agents to maintain her blood pressure. Her CVP increased to 25 to 30 mmHg, her hepatic congestion became aggravated and she developed unpredictable hyperammonemia. Some factors have been shown to have a negative impact on survival after CHLT, such as right ventricular failure, arrhythmia, persistent coagulopathy, and renal failure(9,14). Hence, perioperative care of recipients including the management of surgical complications, and the monitoring and treatment of early hemodynamic, metabolic, and infectious problems, cannot be emphasized strongly enough(19). Pretransplant and posttransplant decision-making and management are critical to achieving good outcomes after CHLT.

Cardiac rejection and allograft vasculopathy were not

evident in patient 2 (case 2) after 4 years of follow-up. In the multiorgan transplantation setting, the liver appears to confer protection against rejection of other organ grafts. The mechanisms underlying this tolerogenic role are not well understood but may involve inducing a state of mixed chimerism, changes in regulatory T cells, or shedding of soluble human leukocyte antigen. The heart is particularly vulnerable to allograft rejection and there is growing evidence that cardiac cellular and antibody-mediated rejection, as well as cardiac allograft vasculopathy, are less frequent after CHLT(20-22).

In conclusion, in carefully selected patients with coexisting heart and liver disease, CHLT can be performed safely at experienced heart and liver transplant centers with low morbidity, low mortality and acceptable long-term patient and graft survival outcomes. Our experiences with this procedure may help guide and encourage future CHLT operations in Korea and in other countries.

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