Outcomes of Adult Liver Transplantation from Donation After Brain Death Followed by Circulatory Death in China

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Background: Organ donation from a deceased donor, which is donation after brain death followed by circulatory death, is a unique transplantation practice in China. Pathological features of grafts help guide the utilization of grafts.

Material/Methods: We retrospectively reviewed our experiences in 188 DBCD allografts from May 2014 to April 2017. We divided 183 transplanted allografts into 3 groups according to pretransplant histology: the good quality graft group (n=62), the preservation injury group (n=27), and the steatotic graft group (n=94). Univariate and multivariate analyses were performed to identify factors in the steatotic graft group predicting the prognoses.

Results: The prevalence rates of allografts in the good quality, steatotic liver, and preservation injury groups were 33.0% (62/188), 50.0% (94/188), and 14.4% (27/188), respectively, and the discarded rate was 2.7% (5/188). The 1- and 3-year overall survival rates were 92.1% and 88.1%, respectively. There were no differences in 1- and 3-year patient survival among the 3 groups (p=0.615). Some complications occurred: acute rejection in 7 cases, lung infection in 11 recipients, biliary stricture and bile leak in 9 patients, and portal thrombosis in 1 recipient; 17 recipients died of various causes. Cox multivariate analysis revealed that longer cold storage time was associated with worse outcome in the steatotic graft group.

Conclusions: Clinical outcomes of adult liver transplantation from deceased donation in China are acceptable.

MeSH Keywords: Biopsy, Fine-Needle • Liver Transplantation • Patient Outcome Assessment • Tissue and Organ Procurement

Abbreviations: DBCD – donation after brain death followed by circulatory death; DBD – donation from brain death; DCD – donation from cardiac death; LT – liver transplantation; MELD – model for end-stage liver disease; HCC – hepatocellular carcinoma

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Background

Liver transplantation (LT) is a widely-accepted treatment alternative for end-stage liver disease (MELD), but the organ supply is far exceeded by demand. Donation after brain death (DBD) is the main source of the organ supply; these organs are continuously perfused through deceased donor heart-beating until deliberately interrupted [1,2], and DBD donors represent more than 80% of the source of organ allografts worldwide, with superior transplant outcomes [3,4]. However, brain death accounts for a small proportion of all-cause mortality, whereas cardiac death is the largest cause of mortality and is the main standard used in the death declaration, especially in China. DBD can potentially expand the donated organ pool. Donation after cardiac death (DCD) has efficiently increased donor supplies from 1% in 1996 to approximately 5% in 2005. DCD is a distinctly different procurement protocol in that organ function is affected by subsequent warm ischemia after the withdrawal of life support [5–9]. Outcomes for liver transplantation from DCD are characterized by higher complication rates, inferior survival, and higher costs in comparison with DBD liver transplantation, especially in light of the higher rate of ischemic-type biliary lesions and subsequently formidable treatments [10,11].

In China there is at present no law about brain death. Cardiac death is the standard determination of death, and donation after brain death followed by cardiac death is the exclusive source of organ [12,13]. Pathology in association with biochemical parameters universally guide the utilization of donated organs, including livers from brain death or cardiac death. Clinical experience with DBCD is limited; here, we report a single-center experience with adult liver transplantation from deceased donors in China.

Material and Methods

From May 2014 through May 2017, 188 donated livers from DBCD (type 3 of Maastricht criteria of donation after cardiac death) were obtained and 183 liver transplantations were performed at the Liver Transplant Center of the 302 Hospital; 62 liver grafts were histologically confirmed as good (good graft group, n=62), 27 liver grafts with various preservation injuries were confirmed (preservation injury graft group, n=27), 94 grafts with different degrees of microvesicular and macrovesicular steatosis were detected (steatotic graft group, n=94), and no re-transplantation was included (Table 1). We distributed the 78 recipients with primary hepatocellular carcinoma (HCC) into 3 groups. Organ evaluation and procurement were undertaken following donation from deceased donors in China, and blood and tissue samples were taken for biochemical testing and histological examination before the transplantation.

The indication for LT was benign end-stage liver diseases and HCC with liver cirrhosis meeting the Hangzhou criteria [14, 15].

Orthotopic liver transplantation was performed with caval replacement, and duct-to-duct choledochocholedochostomy was made without T-tube insertion. Then, the recipients were sent to the Intensive Care Unit (ICU) until life signs were stable and trachea cannulae were extubated [16].

We collected data on donors and recipients, including age, sex, cold storage time, donor risk index, primary disease, blood loss at LT, and MELD score. This study was approved by the 302 Hospital Ethics Committee, and informed consent for DBCD LT was obtained from all recipients or their families. All procedures were in accordance with the ethics standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

Immunosuppression protocol

One dose of Basiliximab was given for induction of immunosuppression, and methylprednisolone was initiated with a 0.5–1.0 g (10 mg/kg) intravenous bolus immediately before or after reperfusion of the hepatic graft and then weaned to 200 mg/day (day 1) at a 40-mg reduction daily to 20 mg/day (day 6). Basic immunosuppression consisted of prednisone, tacrolimus and mycophenolate mofetil (MMF). Prednisone is orally administrated at dose of 1 mg/kg on day 7, tapered at 10 mg per week and maintained at 10 mg within 1 month (11). Tacrolimus was orally administered twice a day on postoperative day 4 at a dose of 0.1 mg/kg, and adjusted to maintain 12-h whole-blood trough levels between 8 and 12 ng/mL for the first month, then 7–10 ng/mL for the next 2 months, followed by 5–8 ng/mL up to the 1st year, and was thereafter maintained at 3–6 ng/mL. MMF was also administered on postoperative day 4 at the dose of 0.75 g twice a day, adjusted by white blood cell counts. Recipients were tested for allograft dysfunction and observed for episodes of acute rejection and the occurrence of opportunistic infection or malignancies. The immunosuppression was adjusted based on these clinical observations, especially on renal functions.

Prophylaxis and treatment of hepatitis B

Combined nucleotide analogue and HBV immunoglobulin was applied indefinitely for prophylaxis of HBV recurrence and resultant antiviral therapy: 4000 u of HBV immunoglobulin was intravenously transfused at the time of LT; for first 3 days, 2000 U was intravenously administered once daily and later once a month; HBV surface antibody level was maintained at 500 IU/L or more for 1 month, at 200 IU/L for the first year, and afterwards it was maintained above 100 IU/L. Nucleotide
Table 1. Characteristics of 183 adult liver transplantations from DBCD.

|                      | Good graft (n=62) | Preservation injury (n=27) | Steatotic graft (n=94) | p    |
|----------------------|-------------------|---------------------------|------------------------|------|
| **Donor**            |                   |                           |                        |      |
| Sex (M/F)            | 52/10             | 24/3                      | 83/11                  | >0.05|
| Age                  | 46.9±11.9         | 48.2±10.8                 | 48.1±11.8              | >0.05|
| Cold ischemic time (h)| 7.5±2.9          | 8.5±3.5                   | 7.4±3.1                | >0.05|
| Total bilirubin (μmol/l) | 14.4±3.3     | 13.2±9.6                  | 13.4±7.1               | >0.05|
| Donor risk index     | 1.31±0.23         | 1.21±0.30                 | 1.27±0.19              | >0.05|
| **Recipient**        |                   |                           |                        |      |
| Sex (M/F)            | 48/14             | 19/8                      | 81/13                  | >0.05|
| Age                  | 49.5±9.4          | 50.7±10.7                 | 49.0±9.9               | >0.05|
| MELD                 | 18.0±10.0         | 19.6±10.9                 | 19.3±10.6              | >0.05|
| **Primary disease**  |                   |                           |                        | >0.05|
| Hepatitis B          | 15                | 3                         | 30                     |      |
| Hepatitis C          | 1                 | 1                         | 2                      |      |
| Alcohol              | 8                 | 3                         | 8                      |      |
| Auto-immune hepatitis| 1                 | 0                         | 2                      |      |
| Drug-induced hepatitis| 2                | 0                         | 0                      |      |
| Wilson disease       | 1                 | 1                         | 1                      |      |
| Spontaneous          | 1                 | 2                         | 7                      |      |
| Other                | 5                 | 2                         | 6                      |      |
| **Malignancy**       | 25                | 15                        | 38                     |      |
| Blood loss (l)       | 1.25              | 1.50                      | 1.625                  | 0.645|
| Tube time (h)        | 15                | 13                        | 14.6                   | 0.296|
| **Main Complications**|                |                           |                        | >0.05|
| Portal thrombosis    | 0                 | 1                         | 0                      |      |
| Hydrothorax          | 4                 | 4                         | 6                      |      |
| Lung infection       | 5                 | 1                         | 5                      |      |
| Biliary              | 1                 | 1                         | 0                      |      |
| Acute rejection      | 6                 | 0                         | 1                      |      |
| Acute renal injury   | 4                 | 0                         | 4                      |      |
| Death                | 5                 | 4                         | 8                      |      |
| **1-year survival rate** | 93.5            | 88.9                      | 91.9                   | 0.615|
| **3-year survival rate** | 88.4            | 82.1                      | 89.8                   |      |
analogue resistance was defined as negative HBV DNA on therapy with subsequent HBV DNA positivity associated with an elevated serum alanine aminotransferase, excluding other causes like inflammation, rejection, and ischemia.

Follow-up

All patients were advised to receive follow-up by surgeons at the Department of Liver Transplantation at the 302 Hospital, with concerns for complications, immunosuppression status, and nutritional, social, and career guidance. For the frequencies of follow-up, once weekly for the first month, once biweekly for the next 2 months, once a month for the next 9 months, and every 3 months thereafter. Liver graft histology was obtained with needle biopsy under ultrasound guidance. All complications were monitored closely and managed promptly.

All of the patients listed for liver transplant at our center were fully informed about the possibility of receiving a DBCD liver and all of them signed the consent form.

Statistical analysis

Donor and recipient characteristics included in these analyses were age, sex, MELD score, donor age, donor risk index, and cold ischemia time. These data are presented as means and medians, and the 2 groups were compared using the t test or the chi-square test. Patient survival curves were estimated using the Kaplan-Meier method and compared using the Wilcoxon test. We used the Cox proportional hazards model to identify factors independently associated with survival in the steatotic graft group. Factors that emerged in the entire cohort with a P value < 0.10 were considered to be significant baseline covariates. They were analyzed by multivariate logistic regression analyses using the forced entry method using the SPSS 22.0 statistical package (SPSS, Inc, Chicago, IL, USA), and a p value of less than 0.05 was set as significance.

Results

As of April 30, 2017, 188 donated livers were procured at the Liver Center of the 302 Hospital. Five grafts were discarded: 1 due to cancer metastasis, 3 due to elevated bilirubin, and 1 due to very severe steatosis. We divided the 183 transplanted livers into 3 groups: the good graft group, the steatotic graft group, and the preservation injury group. In the good graft group, 62 (33.0%) allografts were histologically determined to be good. In the steatotic graft group, steatosis was detected in biopsies of 94 grafts (50%), of which 55 grafts had mild steatosis, 48 had moderate steatosis, and 1 had severe steatosis (60% hepatocytes involved in steatosis), and mixed microvesicular and macrovesicular steatosis was found in 39 allografts [17]. In the preservation injury group, 9 grafts had mild preservation injury and 2 grafts had mild-to-moderate preservation injury; mild hydropic degeneration was confirmed in 5 grafts, mild diffuse hepatocyte swelling in 8 grafts, diffuse hepatocyte swelling in 1 graft, and granulocyte infiltration in the portal zone in 2 grafts. The median follow-up time was 31 months (6–41 months) [19].

Recipient survival

The 1- and 3-year overall survival rates were 92.1% and 88.1% (Figure 1). In the good quality graft group, 1- and 3-year survival rates were 93.5% and 88.4%, respectively; in the preservation injury group, they were 88.9% and 82.1%, respectively; and in the steatotic graft group, they were 91.9% and
89.8%, respectively. There were no differences in patient survival among the 3 groups (p=0.615) (Figure 2).

Complications after transplantation

Transient complications highly responsive to treatments, like headache, dyspepsia, and electrolyte imbalance, were not included in this study. Postoperative complications were closely monitored and promptly managed (Table 1).

Lung infection and thoracic effusion

Lung infection occurred in 11 recipients: 5 patients each in the good graft group and the steatotic graft group, and 1 in the preservation injury group. The pathogens identified were bacteria, fungi, and parvovirus B19. In most cases, infection occurred early after transplantation. Thoracic effusion was detected shortly after LT in 13 recipients, but no surgical intervention was used.

Biliary complications

Biliary stricture occurred in 7 recipients at 1–12 months after LT. ERCP efficiently drained bile in 5 cases, and bile leaked in 2 cases at 1 month after liver transplant (1 each in the good graft group and the preservation injury group). One patient died of septic shock secondary to bile leakage, and 1 patient needed surgical intervention, for which hepatojejunostomy was performed, and it resolved. The rate of biliary complications was 3.83% (7/183).

Acute rejection

Seven recipients had 7 episodes of acute rejection confirmed by fine-needle biopsy. They were treated through bolus injection of steroid, and the grafts then functioned well.

Recrudesces of primary diseases

Twelve recurrences of primary HCC were detected at 1 year after LT. The 1-year recurrence rate of HCC was 15.4% (12/78), and 7 died in the first year. For the recurrence of HCC, Sorafenib was given for no apparent lesion. For elevated AFP, radiofrequency ablation, surgical resection, and transarterial chemoembolization were selectively applied, and no recurrence of HBV was found during follow-up.

Other complications

Acute renal injuries were found in 8 patients and cured before patient discharge by adjusting the nephrotoxicity of the drugs. Portal thrombosis was detected at 1 month after LT in a female recipient with Wilson disease; a stent was placed and her liver graft subsequently functioned well.

Causes of deaths

As of September 2017, 17 recipients were dead: 6 died in the first month after transplantation, 8 died at 3–10 months in the first year, and 3 died 1 year after transplantation. Five patients were from the good-quality graft group, 4 were from the preservation injury group, and 8 were from the steatotic graft group. Lung infection occurred early after LT and caused 4 deaths: the pathogens identified were Aspergillus fumigatus, Enterococcus faecium, Enterococcus asburiae, and Klebsiella pneumonia. Seven recipients died of HCC recurrence, 1 recipient died of cerebral hemorrhage due to graft dysfunction at 6 months, and there was 1 death each due to severe hepatic coma, bile leak, and GVHD. One patient died of de novo carcinoma of the tongue 1 year later. A female recipient died of peritoneal infection due to salpingitis (Table 2). The overall complication rates did not differ significantly among the 3 groups.

Categorical and continuous variables, including recipient age, sex, original disease, graft pathology, MELD score, cold storage time, and blood loss were subjected to univariate analysis, followed by multivariate analyses, to determine the factors associated with prognosis. Cold storage time appeared to be an important influence on outcome in this study (p=0.019, CI 1.065–1.500).

Discussion

Organ shortage is ubiquitous in the field of organ transplantation. The concept of brain death has not been widely accepted in China due to tradition and culture, and the discussion of laws regarding brain death in China is outside the scope of this study [12]. Transplantation of donated organs from deceased donors as the main organ source in China was initiated in the early of 2000s and expanded officially in 2015. A novel organ donation type, namely DBCD, has been created by the Chinese transplant authorities and experts; it is only used in state-accredited hospitals. DBCD is already becoming the main type of deceased organ donation in China. A small number of live donor liver transplants have been conducted in a few centers [13].

The DBCD porcine model was established to define the pathophysiological and biochemical characteristics of the donors; the porcine hemodynamic pattern closely resembles that of humans: DBCD liver allografts have well-organized hepatocyte cords, mild hepatocyte edema and vacuolization, and less parenchymal necrosis [20]. These characteristics are comparable to those of DBD liver allografts. Our study found that the survival rate and complication rate of DBCD LT were comparable to those of DBD LT.
Donor histology may be critical to screen graft viability and to predict early graft functions and patient survival [21]. It is routinely retrieved pretransplant and reassessed by a pathology professional in a blind manner to assess steatosis, inflammation, fibrosis, and injuries. In combination with liver function tests, it guides transplant surgeons in making decisions. In our report, 5 grafts were discarded for use through histological examinations.

It is common in biopsy findings that lipid droplets accumulate as microvesicles, microvesicles, or both in hepatocytes and are referred to as steatosis. It is estimated that the prevalence of steatosis ranges from 6% to 33% with a median of 20% in the general population worldwide [16]. Steatotic liver grafts accounted for more than half of all donors in our study. Many studies, including the present report, have concluded that a graft with mild steatosis (<30%) is generally able to be used, whereas very severe steatosis (>60%) or macrovesicular steatosis of >30% is recognized as an important prognostic factor for graft dysfunction [22]. Lo et al. reported that liver allografts with very severe steatosis could be safely utilized in the setting of DBD with <7-h cold storage time [23,24]. One such graft was transplanted in our report and the outcome was favorable.

In our study, good-quality grafts accounted for about one-third of all liver grafts, while grafts with preservation injuries accounted for about 15% of all grafts. In fact, all grafts will experience some degree of injury during the transplantation process. Histological examination of intraoperative allograft specimens should accurately reveal preexisting diseases and preservation injuries, and no single parameter, biomarker, or test is now in clinical use to effectively predict primary graft dysfunction [17].

We found that preservation injury, including sinusoidal neutrophilic infiltrate and hepatocellular necrosis in the biopsied graft, was rare, and only occurred in a few cases. Our study shows the prognostic value of preservation injury-related histological findings obtained after reperfusion, which can predict postoperative and poor early postoperative recovery. We found that there was no single feature that could be relied on to predict liver function after liver transplantation [18].

| Age/sex | Etiology | MELD | CIT  | Graft* | Time (days) | Cause of death |
|---------|----------|------|------|--------|-------------|----------------|
| 1       | 62/F     | Auto, HCC | 22   | 10     | 10%*        | 378            | Recur, B19     |
| 2       | 61/F     | HBV, HCC | 8    | 10     | Injury§     | 153            | Recur          |
| 3       | 68/M     | HBV, HCC | 7    | 10     | 10%*        | 40             | Lung infection |
| 4       | 45/F     | HBV    | 19   | 11     | 10%*        | 17             | Lung infection |
| 5       | 55/M     | HBV, HCC | 8    | 7.4    | 30%*        | 12             | Lung infection |
| 6       | 29/F     | Drug    | 32   | 4.2    | Normal      | 6              | Hepatic coma   |
| 7       | 35/F     | PBC     | 18   | 14     | 10%*        | 199            | Salpingitis    |
| 8       | 50/M     | HBV    | 14   | 7      | 10%*        | 177            | Graft dysfunction |
| 9       | 51/F     | HBV, HCC | 7    | 8      | Normal      | 81             | Recur          |
| 10      | 62/M     | HBV, HCC | 14   | 13     | Fibrosis    | 434            | Recur          |
| 11      | 58/M     | HBV, HCC | 40   | 9      | Infiltration¥ | 99            | Recur          |
| 12      | 47/M     | HBV, HCC | 47   | 10     | Mixed¥      | 209            | Recur          |
| 13      | 50/M     | HBV, HCC | 40   | 2.3    | Normal      | 165            | Recur          |
| 14      | 57/M     | HBV, HCC | 7    | 5      | Normal      | 544            | De novo cancer |
| 15      | 31/M     | Cirrhosis | 25   | 5      | Diffuse edema£ | 16            | Bile leak      |
| 16      | 62/M     | Alcohol | 27   | 5      | Normal      | 27             | GVHD           |
| 17      | 41/M     | HBV    | 15   | 11     | 10%*        | 282            | Lung infection |

Graft* = liver graft histology; HBV – hepatitis B virus; HCC – hepatocellular carcinoma; Auto – autoimmune hepatitis; MELD – model for end stage liver disease score; PBC – primary sclerosing cholangitis; 10%* – 10% of hepatocytes involved in steatosis; injury§ – mild preservation injury; edema£ – mild diffuse edema; mixed¥ – 20% hepatocytes involved microvesicular and macrovesicular steatosis; GVHD – graft versus host disease; infiltration¥ – moderate infiltration of portal zone.
Liver transplantation is still a technically challenging surgery that often has various complications, including graft-related incidences or complications like primary graft failure, biliary leakage and stricture, and vascular complications [25]. For the recurrences of primary disease like HCC, effective treatment options are limited, and this impedes improving long-term survival and expanding the indications for LT [26]. Short-term outcomes after LT continue to improve as more meticulous transplant procedures are applied. The results of the present study show that lower complication rates can be achieved by consistent and meticulous surgery, and can reach levels comparable to those achieved with the DBD donation protocol [3,4].

Conclusions

LT from donation after deceased donors in China is feasible and acceptable.

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Conflicts of interest

None.

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