Liver Transplantation in Children Using Organ Donation After Circulatory Death
A Case-Control Outcomes Analysis of a 20-Year Experience in a Single Center

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IMPORTANCE While orthotopic liver transplantation (OLT) is a durable life-saving treatment for patients with irreversible liver disease, the waiting list mortality rate for children younger than 6 years is 4 times higher than for children aged 11 to 17 years and adults owing to scarce availability of size-appropriate grafts for transplantation.

OBJECTIVE To compare long-term outcomes for children (aged ≤18 years) undergoing OLT using grafts from donation after circulatory death (DCD) and donation after brain death (DBD).

DESIGN, SETTING, AND PARTICIPANTS Retrospective study using case-control matched groups at a university transplant center. All patients aged 18 years and younger who underwent OLT using DCD organs between February 1, 1990, and November 30, 2010, at the University of California, Los Angeles, were matched in a 1 to 3 ratio with patients who received primary OLT from DBD donors within a 12-month period. Other matching criteria included recipient age, weight, cause of liver disease, and acuity of illness. Outcomes after OLT were compared for DCD (n = 7) and DBD (n = 21) donors. The median follow-up was 4.5 years.

MAIN OUTCOMES AND MEASURES The primary outcome measure was graft failure–free survival; the secondary end point was the development of ischemic cholangiopathy.

RESULTS Comparing DCD and DBD groups, recipient median age (28.4 vs 20.1 months, respectively; P = .80), weight (12.0 vs 11.6 kg, respectively; P = .87), Model for End-Stage Liver Disease/Pediatric End-Stage Liver Disease score (19 vs 11, respectively; P = .48), and donor age (24.0 vs 13.1 months, respectively; P = .72) were similar. For the DCD donors, the median donor warm ischemia duration was 24 minutes. Liver test results were similar for both groups at 1 week and 3, 6, and 12 months following OLT. Ten-year patient and graft survival rates for both DCD and DBD were 100%. Neither ischemic cholangiopathy nor vascular complications occurred in the DCD group. Biliary anastomotic strictures occurred in 1 DCD patient and 3 DBD patients.

CONCLUSIONS AND RELEVANCE Our study showed excellent long-term outcomes with liver transplantation in children using DCD organs. Use of liver grafts procured after circulatory death is an effective approach to expand the donor pool and remains an untapped resource for children with end-stage liver disease.

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Orthotopic liver transplantation (OLT) is a durable life-saving treatment for patients with irreversible liver disease. Donor availability is the principal factor limiting expansion of OLT. This is a particular problem in small children, with scarce availability of size-appropriate grafts. In the current era, the waiting list mortality rate for children younger than 6 years is 4 times higher than for children aged 11 to 17 years.¹

United States law requires that criteria for brain death or circulatory death must be met prior to organ donation for transplantation. Brain death is defined as the irreversible cessation of all brain function including the brainstem, and circulatory death is defined as irreversible cessation of circulation and respiratory functions. Most organs today are retrieved from donors after circulatory death (DBD) donors. In contrast to liver grafts from DBD donors for which blood circulation and organ perfusion are maintained by the beating heart until initiation of organ preservation, organs from donation after circulatory death (DCD) donors are subjected to a period of absent blood flow before cold preservation can be administered.² Diminished quality and function of DCD liver grafts after transplantation have been attributed to an additional warm ischemic insult, which augments organ preservation injury.³⁻⁴

Donation after circulatory death has been used to address the acute shortage of organs and to decrease waiting list mortality. Compared with patients who received DBD grafts, the long-term outcome data in adult recipients have shown inferior survival and higher rates of graft failure and ischemic cholangiopathy (diffuse intrahepatic ductal stricturing) for DCD grafts.⁵⁻¹⁰ At present, the use of DCD grafts for children remains controversial and outcome data are limited. This study was undertaken to compare long-term outcomes after OLT in children using DCD and DBD grafts.

Methods

Data Collection and Study Design

Using a prospectively maintained database, we performed a retrospective analysis of all patients aged 18 years and younger who underwent OLT using DCD organs between February 1, 1990, and November 30, 2010, at the University of California, Los Angeles (UCLA). This cohort of transplant recipients was matched in a 1 to 3 ratio with patients who received primary OLT from DBD donors within a 12-month period. The matching criteria included recipient age, weight, cause of liver disease, and acuity of illness.¹¹ Recipients who received partial grafts or multiorgan transplants were excluded. The median follow-up was 4.5 years. The UCLA Institutional Review Board approved the study. The requirement for written informed consent was formally waived because this was a retrospective study. Outcomes after OLT were compared for DCD (n = 7) and DBD (n = 21) donors.

Definition of Ischemia Times and Operative Variables

A timeline of the phases of ischemic injuries for organs procured after circulatory death and brain death is shown in the Figure. Compared with grafts procured after DBD, the DCD organs are subjected to an additional warm ischemic insult on cessation of life support. The donor warm ischemia time is defined as the interval from withdrawal of life support to initiation of cold organ preservation, graft cold ischemia time as the interval from initiation of in vivo cold organ preservation to removal of the graft from 4°C cold storage, and graft warm ischemia time as the interval from removal from cold storage to reperfusion of the liver graft.

Deceased Donor Selection and Protocol

The deceased selection and organ procurement procedures used the UCLA protocols and techniques for DCD and DBD.¹²⁻¹⁴ The DCD donor selection process followed stringent screening criteria: for donor, age younger than 45 years, body mass index (calculated as weight in kilograms divided by height in meters squared) less than 30, hospitalization for 5 or fewer days, and preprocurement serum liver transaminase levels less than twice the normal values at the time of organ acceptance and procurement; for graft, projected duration of organ cold ischemia time less than 8 hours, excellent liver parenchymal quality on intraoperative assessment, and donor warm ischemia time less than 30 minutes.¹⁵

The DCD procurement protocol followed Institute of Medicine guidelines.¹⁶ Artificial life support was withdrawn in the operating room or intensive care unit. Systemic heparin was administered prior to withdrawal of life support if the policies of the organ procurement organizations or donor hospital permitted its use. An independent physician from the donor hospital was assigned to provide end-of-life care, withdraw life support, and declare death.

Following a 5-minute mandatory waiting period after asystole to ensure that autoresuscitation did not occur, a rapid procurement technique was performed and cold organ preservation with University of Wisconsin solution (4–6 L) was initiated via the infrarenal aorta.¹⁶ A vascular clamp was applied on the thoracic aorta to confine the circulation of the cold organ preservation solution within the abdominal organs. An incision at the right atrium allowed drainage of blood and effluent fluid. Cold organ preservation solution was also delivered to the portal venous system via the inferior mesenteric vein. Once the
cold organ preservation solution was delivered to the abdominal organs and external organ cooling was achieved, the common bile duct was immediately accessed and University of Wisconsin solution was flushed into the biliary system. Organs were stored in University of Wisconsin solution at 4°C for transport. Beginning in 2006, we initiated a center protocol of administering tissue plasminogen activator to all DCD livers before implantation. Tissue plasminogen activator, in a total dose of 2 mg in 100 mL of sterile water, was injected into the donor hepatic artery on the back table and maintained within the arterial system by a vascular clamp on the artery until vascular anastomosis occurred.

Patient Selection and Operative Procedure

Patients diagnosed as having end-stage liver disease were evaluated by a multidisciplinary team as previously described.9 Before 2002, patients were listed for liver transplant candidacy according to the United Network for Organ Sharing status categories; from 2002 to present, the current Model for End-Stage Liver Disease/Pediatric End-Stage Liver Disease (MELD/PELD) system has been used.10 For patients aged 12 years and older, the MELD scores were calculated on the basis of serum creatinine level, total bilirubin level, and international normalized ratio at the time of OLT. For younger patients (aged <12 years), variables used for PELD scores were serum albumin level, total bilirubin level, international normalized ratio, growth failure (based on sex, weight, and height), and age at listing. The MELD/PELD scoring system ranks children according to their probability of death within 3 months of listing without a liver transplant. A MELD/PELD score of 40 or higher predicts a waiting list mortality of 100%. In this study, the laboratory MELD/PELD scores were used for the analysis. The surgical procedure for OLT was performed in a standard manner as previously described.77

Recipient, Donor, and Operative Variables

Variables collected for analysis included the following: for both recipients and donors, age, race/ethnicity, sex, height, and body weight; for recipients, primary liver disease, MELD/PELD score, and liver test results 1 week and 3, 6, and 12 months following OLT (including serum alanine aminotransferase level, aspartate aminotransferase level, alkaline phosphatase level, total bilirubin level, and international normalized ratio); and for donors, duration of hospitalization before donation, cause of death, need for vasopressors prior to donation, and donor warm ischemia time. Operative variables included graft cold and warm ischemia times.

Outcome Measures

The primary end point was 10-year graft failure–free survival. Graft failure was defined as either the need for retransplantation or death due to primary graft nonfunction or biliary complication. Secondary outcome measures focused on biliary complications, either ischemic cholangiopathy or anastomotic stricture, and vascular complications.

Statistical Analysis

Graft failure–free patient survival curves were computed using Kaplan-Meier methods and compared using log-rank tests. Medians and interquartile ranges of continuous variables were compared using Wilcoxon rank sum test, and proportions of categorical variables were compared using χ² test. Statistical analysis was performed using SAS version 9.1 statistical software (SAS Institute, Inc).

Results

Recipient Characteristics and Severity of Illness

Age, weight, and indications for OLT were similar for both groups (Table 1). The most common cause of end-stage liver disease was biliary atresia, followed by acute liver failure, neonatal hepatitis, malignant neoplasm, and other diseases. Regarding acuity of illness at the time of OLT, the median MELD/PELD score was 19 for the DCD group and 11 for the DBD group (P = .48). The proportion of recipients who required urgent OLT for acute liver failure did not differ between groups.

Donor Characteristics and Ischemia Duration

Age, weight, sex, cold ischemia time, and warm ischemia time were similar for both groups (Table 2). The median donor age was 24.0 months for DCD and 13.1 months for DBD (P = .72). For the DCD donors, the median donor warm ischemia duration was 24 minutes.

Table 1. Recipient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Donation After Circulatory Death (n = 7)</th>
<th>Donation After Brain Death (n = 21)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), mo</td>
<td>28.4 (9.6 to 59.2)</td>
<td>20.1 (11.0 to 31.1)</td>
<td>.80</td>
</tr>
<tr>
<td>Weight, median (IQR), kg</td>
<td>12.0 (7.6 to 18.3)</td>
<td>11.6 (6.9 to 12.8)</td>
<td>.87</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>3 (42.9)</td>
<td>9 (42.9)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Liver disease diagnosis, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biliary atresia</td>
<td>3 (42.9)</td>
<td>9 (42.9)</td>
<td></td>
</tr>
<tr>
<td>Acute liver failure</td>
<td>1 (14.3)</td>
<td>3 (14.3)</td>
<td>.90</td>
</tr>
<tr>
<td>Neonatal hepatitis</td>
<td>1 (14.3)</td>
<td>3 (14.3)</td>
<td></td>
</tr>
<tr>
<td>Malignant neoplasm</td>
<td>1 (14.3)</td>
<td>3 (14.3)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (14.3)</td>
<td>3 (14.3)</td>
<td></td>
</tr>
<tr>
<td>MELD/PELD score, median (IQR)</td>
<td>19 (~1 to 30)</td>
<td>11 (~4 to 21)</td>
<td>.48</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; MELD/PELD, Model for End-Stage Liver Disease/Pediatric End-Stage Liver Disease.
Liver Function, Survival Analysis, and Morbidity

Liver test results (Table 3) were compared for the 2 groups at various intervals after OLT. Median peak levels of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and total bilirubin were similar at 1 week and 3, 6, and 12 months.

The 10-year graft failure–free survivals after OLT were 100% in both DCD and DBD groups. No primary graft nonfunction was observed in either group. Biliary and vascular complications were infrequent in both groups. Anastomotic biliary stricture occurred in 4 patients, 1 after DCD and 3 after DBD. Ischemic cholangiopathy did not occur in either group. There were no arterial complications; portal vein thrombosis occurred in 1 patient in the DCD group and none in the DCD group. There were no retransplantations.

Discussion

While liver grafts procured after circulatory death have been used to expand the donor pool in adults, there has been reluctance to use this potential organ resource in children. In 2011, only 3 of 474 children (0.6%) in the United States received OLT from DCD donors. Limited use of DCD organs may be owing to the inferior outcomes and higher rates of graft failure and ischemic cholangiopathy reported with grafts from DCD in adult transplantation. Notwithstanding these complications, DCD liver grafts are precious life-saving organs that can reduce waiting list deaths and have been reported to provide survival benefits in selected patients.14,19-22 Our study was undertaken to compare long-term outcomes for OLT using DCD and DBD donors in children.

Our study shows excellent long-term graft failure–free outcomes with liver transplantation in children using DCD organs. Similar to our experience, another single center reported excellent patient and graft survival in children at a median follow-up of 42 months.23 These findings suggest that outcomes after OLT using DCD grafts in children differ from those in adults. Analysis of the United Network of Organ Sharing database in adult OLT with DCD grafts reported an 85% higher risk for graft failure and a need for retransplantation in 21.6% of patients, compared with 8.8% of patients with DBD grafts.8,10 In contrast, using the same national registry data, Abt et al reported rates of primary graft nonfunction as 5.3%

### Table 2. Donor Characteristics and Graft Ischemia Duration

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Donation After Circulatory Death (n = 7)</th>
<th>Donation After Brain Death (n = 21)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), mo</td>
<td>24.0 (3.0-72.0)</td>
<td>13.1 (2.0-48.0)</td>
<td>.72</td>
</tr>
<tr>
<td>Weight, median (IQR), kg</td>
<td>12.0 (8.6-23.0)</td>
<td>11.0 (6.1-15.0)</td>
<td>.88</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>4 (57.1)</td>
<td>12 (57.1)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Donor warm ischemia, median (IQR), min</td>
<td>24 (18-29)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Graft cold ischemia</td>
<td>300 (240-420)</td>
<td>420 (240-540)</td>
<td>.41</td>
</tr>
<tr>
<td>Graft warm ischemia</td>
<td>39 (32-42)</td>
<td>44 (37-48)</td>
<td>.13</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; NA, not applicable.

### Table 3. Comparison of Liver Function Test Results Between Donation After Circulatory Death and Donation After Brain Death Grafts at Different Intervals After Liver Transplantation

<table>
<thead>
<tr>
<th>LFT</th>
<th>Post-OLT Interval</th>
<th>1 wk</th>
<th>3 mo</th>
<th>6 mo</th>
<th>12 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>P Value</td>
<td>Median (IQR)</td>
<td>P Value</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCD</td>
<td>421 (329-1235)</td>
<td>.26</td>
<td>17 (12-79)</td>
<td>.75</td>
<td>18 (9-50)</td>
</tr>
<tr>
<td>DBD</td>
<td>491 (120-785)</td>
<td></td>
<td>19 (16-33)</td>
<td></td>
<td>21 (16-39)</td>
</tr>
<tr>
<td>AST, U/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCD</td>
<td>635 (525-2925)</td>
<td>.48</td>
<td>26 (20-44)</td>
<td>.34</td>
<td>28 (22-46)</td>
</tr>
<tr>
<td>DBD</td>
<td>902 (226-1197)</td>
<td></td>
<td>34 (27-47)</td>
<td></td>
<td>31 (26-40)</td>
</tr>
<tr>
<td>TB, mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCD</td>
<td>9.8 (4.6-11.2)</td>
<td>.36</td>
<td>0.4 (0.2-0.6)</td>
<td>.59</td>
<td>0.4 (0.3-0.9)</td>
</tr>
<tr>
<td>DBD</td>
<td>4.9 (1.0-20.1)</td>
<td></td>
<td>0.4 (0.3-0.6)</td>
<td></td>
<td>0.5 (0.4-0.7)</td>
</tr>
<tr>
<td>AP, U/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCD</td>
<td>198 (121-380)</td>
<td>.14</td>
<td>214 (181-301)</td>
<td>.62</td>
<td>222 (190-238)</td>
</tr>
<tr>
<td>DBD</td>
<td>147 (77-217)</td>
<td></td>
<td>185 (124-243)</td>
<td></td>
<td>191 (126-254)</td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; DBD, donation after brain death; DCD, donation after circulatory death; IQR, interquartile range; LFT, liver function test; OLT, orthotopic liver transplantation; TB, total bilirubin.

SI conversion factors: To convert ALT, AP, and AST to microkatal per liter, multiply by 0.0167; to convert TB to micromoles per liter, multiply by 17.104.
Liver Transplantation in Children

Original Investigation Research

Our study supports the use of pediatric DCD grafts in children 11 to 17 years of age, which may be appropriate for small children, owing to the scarcity of available size-appropriate grafts. If the rate of transplantation remains limited, the initial results are superior compared with 0.2% in adult recipients of DBD grafts. Cold ischemic organ preservation has been shown to avert the adverse effects of donor warm ischemia in the development of ischemic cholangiopathy. Ischemic cholangiopathy did not develop in children in this study or in a previous study. A possible explanation is that the biliary epithelium in children is more resilient to ischemia and reperfusion injury.

In summary, our study showed excellent long-term patient survival with liver transplantation using DCD organs in children. Use of liver grafts procured after circulatory death is an effective approach to expand the donor pool and remains an untapped resource for children in need of liver transplantation.

Critical revision of the manuscript for important intellectual content: Hong, Venick, Yersiz, Kositamongkol, Kaldas, Hiatt. Drafting of the manuscript: Hong, Venick, Kaldas, Hiatt. Critical revision of the manuscript for important intellectual content: Hong, Venick, Kaldas, Hiatt. Critical revision of the manuscript for important intellectual content: Hong, Venick, Yersiz, Kositamongkol, Petrowsky, Farmer, Agopian, McDiamid, Hiatt, Busuttil.

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REFERENCES


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