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SIMULTANEOUS LIVER AND KIDNEY TRANSPLANTATION FROM DONATION AFTER CARDIAC DEATH DONORS: A BRIEF REPORT

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Abstract

Although the use of donation after cardiac death (DCD) donor organs have been shown to be a viable option for liver and kidney transplant recipients, outcomes after simultaneous liver and kidney (SLK) transplantation from DCD donors are less clear. Methods: We performed a retrospective analysis of 37 adult, primary, SLK transplants performed at our center between 1/1/1998 and 12/31/2008. Results: Thirty-two patients received DBD organs and 5 patients received DCD organs. SLK recipients in each group were similar in regard to age, gender, race, BMI, donor race, and donor BMI. Calculated MELD scores and pretransplant GFRs were similar between groups. DCD donors were younger and had a shorter liver cold ischemic time. Median DCD donor warm ischemic time was 19.0 min (6.0–25.0). Recipient surgical time and hospital length of stay were comparable between groups. Delayed graft function was higher in DCD renal allografts (80% vs. 31%, p=0.06). One-year graft survival for liver (DCD: 100% vs. DBD: 94%) and kidney (DCD: 100% vs. DBD: 94%) allografts were similar. Conclusion: Patients undergoing DCD SLK have comparable one- year patient and graft survival and acceptable perioperative morbidity compared to DBD SLK recipients. Although long-term outcomes remain unknown, the utilization of DCD organs for SLK transplantation should be considered as a valid approach to safely expanding the donor organ pool.

Keywords

surgical technique

The utilization of donor organs from DCD donors has been shown to be a viable option for liver transplantation, with acceptable patient and allograft survival despite an increase in biliary complications.(1–3) The introduction of the model for end-stage liver disease (MELD) allocation system has favored liver transplantation in patients with hepatorenal syndrome and/or end-stage renal disease (ESRD). As a result, the frequency of simultaneous liver-kidney (SLK) transplantation has concomitantly increased.(4) The recent consensus conference jointly sponsored by UNOS, the American Society of Transplant Surgeons, the American Society of Transplantation, and the American Society of Nephrology favored simultaneous liver-kidney transplantation in patients with 1) ESRD with cirrhosis and symptomatic portal hypertension or hepatic vein wedge pressure ≥ 10mm Hg, 2) liver failure and chronic kidney disease (CKD) with glomerular filtration rate (GFR) ≤ 30 ml/min, 3) hepatorenal syndrome or acute kidney injury with creatinine ≥ 2.0 mg/dl and dialysis ≥ 8 weeks or 4) liver failure with renal biopsy showing > 30% glomerulosclerosis or

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30% fibrosis.(4) This has increased the number of patients undergoing SLK transplantation, without an associated increase in suitable organ donors.

We have recently published our experience with DCD liver transplantation,(1) DCD kidney transplantation,(5) and our overall institutional outcomes utilizing DCD donors(6). In addition, we have recently published our institution's experience with SLK transplantation.(7) Several studies have estimated the favorable impact that DCD organs could have on the existing donor pool.(8–10) DCD transplantation has increased nationwide in recent years,(8, 11, 12) but still remains below its estimated potential.(13, 14) Our institutional results have prompted consideration of simultaneous liver-kidney transplantation from DCD donors. To the best of our knowledge there are no previous reports describing outcomes of SLK from DCD donors. The purpose of our analysis was to compare the outcomes of SLK transplantation using organs from DCD and donation after brain death (DBD) donors.

METHODS

After Institutional Review Board approval was obtained, we performed a retrospective review of all adult, primary, deceased-donor, SLK transplants (n=37) performed between January 1, 1998 and December 31, 2008. We utilized the prospectively-collected transplant database at the University of Wisconsin. Outcomes were compared between recipients of DBD (n=32) and DCD organs (n=5).

All patients received dexamethasone or methylprednisolone at the time of implantation, and the majority was maintained on mycophenolate mofetil (CellCept, Roche) or mycophenolic acid (Myfortic, Novartis), steroids, and a calcineurin-inhibitor (CNI) (n=32). The remaining patients were maintained on either steroids and a CNI (n=3) or steroids and mycophenolate mofetil (n=2). Induction therapy with either basiliximab (Simulect, Novartis, n=26), anti-thymocyte globulin (Thymoglobulin, Genzyme, n=3) or alemtuzumab (Campath-1H, ILEX, n=2) was used at the discretion of the surgeon. Tacrolimus (Prograf, Fujisawa) was utilized in nearly all cases (n=34), with cyclosporine (Neoral, Novartis) given in only one patient. Steroids were tapered during the transplant hospitalization to prednisone 30 mg/day. This dose was further tapered over the first postoperative months to a baseline of 5–10 mg/day. Presently, SLK recipients receive basiliximab induction and are maintained on mycophenolic acid, tacrolimus, and low-dose prednisone post-operatively.

The primary endpoints in this study were patient and graft survival. MELD score was calculated for all patients including those in the pre-MELD era based on total bilirubin, INR and creatinine. Glomerular filtration rate (GFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation.(15) Unexplained elevations in liver function tests were initially evaluated with duplex ultrasonography of the liver allograft to assess vascular patency. If hepatic vascular flow was normal, percutaneous liver biopsy was performed and evaluated using hematoxylin and eosin staining. Renal biopsies were performed in patients with a creatinine elevated at least 20% above baseline, and were evaluated using hematoxylin and eosin staining per the Banff Criteria. Delayed kidney allograft function was defined as requiring hemodialysis within the first 7 days of transplantation. Mean follow-up in DCD recipients was 1.8±2.2 years, as compared to 3.5±2.6 years in DBD recipients.

Statistical analysis was performed with SAS software. Data are presented as median values with ranges. Rates of rejection, rates of biliary complications, and patient and graft survival rates were estimated using Kaplan-Meier analysis. Group comparisons were performed using a log-rank test. Continuous variables were compared using the Wilcoxon rank sum test and discrete variables were compared using the Fisher's exact test. P-values < 0.05 were considered significant.

DCD procurement technique

Our DCD organ recovery technique has been previously described. (16) To minimize warm ischemic time we routinely obtain additional informed consent for the placement of femoral arterial and venous cannulas under local anesthesia. After declaration of death we begin flushing through the femoral arterial cannula with University of Wisconsin solution and begin venous venting through the venous cannula. We then proceed with rapid opening of the abdomen and chest. The supraceliac aorta is cross clamped and the IVC is vented in the chest. All organs are removed en bloc to the back table where the portal vein is flushed with additional UW solution and the common bile duct is irrigated until clear. The organs are transported back to the University of Wisconsin and separated in cold preservative solution on the back table.

Simultaneous liver-kidney transplantation technique

The liver transplant during SLK transplantation is performed using standard piggyback techniques with vena caval anastomosis to the common orifices of the three hepatic veins. As we have gained experience with SLK transplantation using DCD donors, we have modified our technique slightly. After the vena caval and portal venous anastomoses are completed, the liver is flushed with 1L lactated Ringer's with 2 ampules of 25% albumin to eliminate the residual UW preservation solution. The donor liver is then reperfused through the portal vein. To decrease the incidence of severe post reperfusion syndrome, we now perform an additional 300 cc blood flush of the liver through the infrahepatic IVC. The clamp of the suprahepatic IVC just below the anastomosis is released, restoring the liver outflow, and the infrahepatic IVC is ligated. The hepatic artery anastomosis is then completed.

A meticulous search for hemostasis and surgical bleeding is performed. The perihepatic dissection areas are packed and the subcostal incision is closed with towel clamps. The renal transplant is then performed via a separate right lower quadrant incision using the iliac vessels and standard techniques. After revascularization of the kidney and the completion of the neoureterocystostomy, attention is returned to the liver transplant. Once hemostasis is satisfactory, the biliary anastomosis is performed, typically with an end-to-end choledochocholedochostomy. All anastomoses are again inspected and both wounds are closed once adequate hemostasis is obtained. By using this procedural sequence, we are able to evacuate any perihepatic hematomas that have developed during the kidney transplant without having to reopen the liver transplant incision. Both transplants are typically performed by the same team.

RESULTS

Donor demographics

There were no differences in race, gender, or BMI (DCD: 26.8 kg/m^2 (21.5–43.0) DBD: 28.9 kg/m^2 (19.8–42.5) p=0.89) of the donors between the two groups. DCD donors were significantly younger than DBD donors (Table 1). As expected, the donor warm ischemic time, defined as the time between withdrawal of support and organ flush with preservation solution, was significantly longer in DCD donors (19.0 min (6.0–25.0) $p < 0.0001$) compared to DBD donors.

Recipient demographics

SLK recipients in each group were similar in regard to age, gender, race, and BMI. There were no significant differences in the calculated MELD score, pretransplant creatinine, or calculated GFR using the MDRD equation (Table 1). There was no difference in the rate of hepatorenal syndrome between the groups (DCD:60%, DBD:53%, p=1.00)

There were no differences in the recipient diagnoses of liver disease between the groups. The primary indications for liver transplantation in DCD recipients were steatohepatitis (n=3) and alcoholic liver disease (n=2). Indications for transplantation in DBD recipients included hepatitis C (n=9), alcoholic liver disease (n=8), cryptogenic/steatohepatitis (n=5), alpha-one anti-trypsin deficiency (n=2), and other (n=8) (p= 0.36).

There were no differences in the recipient diagnoses of kidney disease between the two groups. The primary indications for kidney transplantation in the DCD recipients were hepatorenal syndrome (n=3), hypertension (n=1), and type 2 diabetes (n=2). Indications for kidney transplantation in the DBD recipients were hepatorenal syndrome (n=11), unknown etiology (n=5), type 2 diabetes (n=5), hypertension (n=3), IgA nephropathy (n=2), membranoproliferative glomerulonephritis (n=2), acute tubular necrosis (n=2), polycystic kidney disease (n=1), and primary hyperoxaluria (n=1) (p=0.64)

Transplant Outcomes

There was no difference in the requirement for perioperative blood product utilization between the groups. Cold ischemic time for the liver was significantly longer in the DBD group. However total operative time and cold ischemic time for the kidney was not statistically different between recipients of DCD and DBD organs (Table 1).

One DCD recipient required reoperation on post-operative day (POD) 11 for liver debridement of necrotic parenchyma related to premortem donor liver trauma. Another patient required ERCP for an anastomotic biliary stricture on POD 164. No additional operative or percutaneous interventions were required in the first 180 days in any DCD recipient. This compares favorably to a reoperation rate of 25% in the first 30 days following DBD SLK transplantation. Indications for reoperation were bleeding (n=4), lymphocele drainage (n=2), ureteral leak (n=1), and bile leak (n=1)

Delayed renal allograft function (DGF) was defined as the need for dialysis in the first week after transplantation. DGF occurred more frequently in DCD recipients compared to DBD recipients, 80% vs. 31%, p=0.06. Creatinine at the time of discharge was greater in SLK recipients of DCD organs (2.7±1.9 mg/dl when compared to SLK recipients of DBD organs (1.3±0.4 mg/dl), though these differences were not statistically significant (p=0.19). The calculated GFR at 6 months following transplantation was equivalent (DCD: 54 ml/min/1.73m^2, DBD: 56 ml/min/1.73m^2, p=0.81). In addition, length of stay was comparable between DCD and DBD groups (Table 1).

Patient and Graft Survival

One year DCD liver and renal allograft survival was 100% and 100%, as compared to 94% and 94% (p=0.42, p=0.45) for DBD recipients. One DCD SLK recipient experienced rejection of the liver allograft in the first year, and one experienced rejection of the kidney allograft. Thirty-seven percent of DBD SLK recipients experienced rejection of their liver allograft, and 17% rejected their renal allograft, within the same time period. Patient survival at one year from DCD SLK was 100% versus 97% for DBD recipients (p=0.49).

Cause of allograft failure

At most recent follow-up, all DCD recipients were alive with functioning liver and renal allografts. At the same point, in the DBD cohort, 7 liver and 6 renal allografts had failed. Causes of liver allograft failure in this group included death with a functioning graft (n=3), primary non-function (n=2), recurrent disease (n=1), and unknown (n=1). Causes of renal allograft loss included death with a functioning graft (n=4), primary nonfunction (n=1), and unknown (n=1).

Cause of death

Six patients in the DBD group expired during the study period. The causes of death included infection (n=2), cardiac (n=1), recurrent hepatitis C (n=1), malignancy (n=1), and unknown (n=1).

DISCUSSION

The shortage of suitable organ donors for patients in need of liver transplantation provides an impetus to utilize organs from appropriately selected DCD donors despite a higher incidence of biliary complications. As greater emphasis is placed on allocation to patients with renal dysfunction in the MELD system, an increasing number of patients are undergoing SLK transplantation. Although experience with DCD transplantation is accruing at large centers,(1–3, 17) there are no published studies on the outcomes of SLK transplantation from DCD donors. This brief report is the first analysis comparing the outcomes of SLK recipients of DCD organs to those of DBD organs. Our results show that SLK transplantation using livers and kidneys from DCD donors is feasible with acceptable morbidity and mortality rates.

Our institutional policy generally limits DCD liver donation to donors less than 50 years of age and limits warm ischemic time to less than 30 minutes. In this cohort, the average donor was 32 years old, and warm ischemic time was 19 minutes. Additional efforts were made to maximally cool and flush the donor organs with the super-rapid DCD procurement, minimal in-situ dissection, and back-table organ separation only after the organs have significantly cooled during transport to the recipient center. The cold ischemic time for the liver was significantly lower in the DCD vs. DBD group. We strongly believe that prolonged cold ischemic times have a significant negative impact on outcomes after DCD liver transplantation. Therefore, in order to minimize cold ischemic time, the recipient is brought to the operating room prior to the return of the donor organs and the back table preparation of the donor organs and the recipient hepatectomy are performed simultaneously. In addition, we do not perform liver retransplantation with DCD livers due to the likely increased cold ischemic time associated with a difficult hepatectomy. The practice of implanting the kidney prior to closing the liver incision also provides a “second-look” procedure, which may help explain the low reoperation rate in DCD SLK recipients.

Four of the five DCD SLK transplants occurred in the last 2 years of the study period (2007–2008). This reflects a greater comfort and experience with DCD transplantation at our center. This limits the duration of follow-up in these patients, and these results must be interpreted as an early, preliminary report. Although there have been no major technical changes to our liver transplantation technique or strategy, there may be a time bias against the DBD SLK group, as transplants in this group of recipients were distributed more evenly across the 10-year study period. Furthermore, the majority of DCD SLK transplants occurred after our center had significant experience with DCD procurement and transplantation, eliminating the early learning curve associated with novel techniques.

In our earlier series of DCD liver transplantation, the vast majority of biliary and other technical complications occurred within the first 180 days of transplantation and would be captured in this study.(1) In our recent review of 87 DCD liver transplant recipients, 83% of biliary complications occurred in the first 120 days after transplant (Foley DP, et. al. Annals of Surgery, in press). No patients in our present series developed ischemic cholangiopathy, which is almost certainly secondary to the low number of DCD SLK recipients reported. One patient required a single endoscopic intervention to treat an anastomotic biliary stricture. Although the low rate of biliary complications in our small group of SLK

recipients is encouraging, it is expected that more difficulties will be encountered as our experience grows.

Patients undergoing DCD SLK transplantation have comparable one-year survival and acceptable perioperative morbidity, as compared to those undergoing DBD SLK transplantation. Although the rate of delayed renal allograft function is significantly higher in the DCD SLK recipient, this had no long-term impact on liver allograft, renal allograft, or patient survival. These outcomes are similar to our previous analysis demonstrating higher rates of DGF in DCD renal allograft recipients as compared to DBD allograft recipients, but with no difference in long-term allograft survival. (5)

As the number of patients waitlisted for SLK transplantation increases, there will continue to be a need to expand the donor pool using less than ideal allografts for transplantation. Due to the small sample size of each group in this analysis, we are limited in our ability to make projections on what others may encounter with DCD SLK transplants. However, our data demonstrate the feasibility of SLK from DCD donors with comparable short-term results to SLK from DBD donors. Although the long-term results of SLK transplantation using DCD donors remain unknown, the utilization of DCD organs for SLK transplantation is another strategy to minimize the disparity between organ supply and demand while simultaneously yielding acceptable outcomes for patients with end-stage liver and kidney disease.

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Abbreviations

DCD	donation after cardiac death
SLK	simultaneous liver and kidney
DBD	donation after brain death
BMI	body-mass index
MELD	model for end-stage liver disease
GFR	glomerular filtration rate
ERCP	endoscopic retrograde cholangiopancreatography
ESRD	end-stage renal disease
UNOS	United Network for Organ Sharing
CKD	chronic kidney disease
CNI	calcineurin inhibitor
CMV	cytomegalovirus
MDRD	modification of diet in renal disease
UW	University of Wisconsin
GIA	gastrointestinal anastomosis

POD	post-operative day
PRBC	packed red blood cells
FFP	fresh frozen plasma
ICU	intensive care unit

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Table 1
Demographics and Outcomes after SLK Transplantation

Data are presented as median values with ranges.

	DCD (n = 5)	DBD (n=32)	p-value
Donor age (years)	35.0 (20.0–40.0)	45.5 (19.0–68.0)	**0.04***
Recipient age (years)	47.0 (34.5–61.1)	54.4 (20.9–69.8)	0.34
Calculated MELD	33.0 (19.0–44.0)	25.0 (15.0–49.0)	0.18
Recipient BMI (kg/m^2)	35.6 (20.1–44.5)	29.5 (18.9–41.2)	0.24
Creatinine at transplant (mg/dl)	3.7 (1.7–5.5)	3.1 (0.8–6.2)	0.79
GFR at transplant (ml/min/1.73m^2)	14.5 (8.9–34.2)	22.0 (8.0–105)	0.81
Warm ischemic time (min)	19.0 (6.0–25.0)	0	**< 0.0001***
Cold ischemic time: liver (hours)	4.6 (4.0–8.0)	8.0 (2.0–11.3)	**0.03***
Cold ischemic time: kidney (hours)	12.5 (8.2–16.6)	12.5 (6.8–19.6)	0.81
Operative time (hours)	9.9 (8.9–13.1)	9.2 (5.9–15.7)	0.36
Discharge creatinine (mg/dl)	2.1 (0.7–4.8)	1.2 (0.6–2.6)	0.19
Length of stay (days)	19.0 (10.0–29.0)	17.0 (5.0–47.0)	0.76

* P values < 0.05 are considered significant.