Donation after circulatory arrest (DCD) in pancreas transplantation:

A report of 10 cases

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Abstract

Introduction

Transplantation of pancreas allografts procured from donation after circulatory death (DCD) remains uncommon. This study reviews a series of pancreas transplants at a single center to assess the donor and recipient characteristics for DCD pancreas transplant, and to compare clinical outcomes.

Methods

DCD procurement was performed with a 5-minute wait time from pronouncement of death to first incision. In two patients, tissue plasminogen activator was infused as a thrombolytic during the donor flush. All kidney grafts were placed on pulsatile perfusion.

Results

There were 606 deceased donor pancreas transplants, 596 standard donors and 10 DCD donors. Of the 10 DCD transplants, 6 were simultaneous pancreas-kidney and 4 were pancreas transplant alone. The average time from incision to aortic cannulation was less than 3 minutes. The median total ischemia time for the DCD grafts was 5.4 hours, compared to 8.0 hours for standard donors (p=0.15). Median length of hospital stay was 7 days for both groups, and there were no episode of acute cellular rejection in the first year post-transplant for the DCD group (4.2 % for standard group, p=0.65). There was no difference in early or late graft survival, with 100% graft survival in the DCD group up to 1-year post transplant. Ten-year Kaplan-Meier analysis shows similar graft survival for the two groups (p=0.92).

Conclusions

These results support the routine use of carefully selected DCD pancreas donors. There were no differences in graft function, post-operative complications, and early and late graft survival.

Pancreas transplantation (PT) remains the treatment of choice for select candidates with diabetes, particularly type 1 and most commonly in association with a simultaneous kidney transplantation for end stage diabetic nephropathy. [1] However, because the procedure carries potential risk for life-threatening complications after transplant, pancreata undergo strict selection criteria to minimize the risk-benefit ratio associated with the procedure. [2, 3] Yet, like livers and kidneys, the supply of pancreata continues to fall further behind the demand, and this phenomenon can be traced back in part to the strict selection criteria that limit their use to roughly 20% of consented donors. [4-9] This ever-growing gap between the number of patients requiring transplants and the availability of suitable organs has spurred a search for ways to effectively increase the usable organ pool without sacrificing organ quality and increasing adverse events such as delayed graft function (DGF), technical complications andgraft rejection. One such method is increased utilization of the largely unused pool of donors who expire via cardiac/circulatory death. The use of these extended criteria organ donors has successfully increased the number of grafts available for transplantation. [10, 11] In contrast to liver grafts which show definitively that DCD livers may perform worse than standard (DBD) donors [12], investigators have found similar functioning of DCD kidney grafts compared to standard grafts. [13, 14] Pancreas transplants in particular have a limited but growing amount of data regarding the difference between DCD and DBD functioning. Transplantation of pancreas grafts procured from donation after cardiac death (DCD) has been reported but remains uncommon. [10, 11, 15, 16] It has long been believed that due to the high sensitivity of the pancreas to ischemic insult, that DCD pancreata should be avoided and this belief is evident in the data. [2, 3, 9, 17-19] Outcomes for these grafts are still not well described in the literature and few studies extend beyond 5 year follow-up. However, recent studies from Muthusamy et. al., Qureshi et. al., Shahrestani et. al.,

and others are demonstrating that with proper protocols, DCD graft function can be on par with that of DBD grafts at 5 years. [13, 14, 17, 20, 21] This surprising trend is supported by our findings which extend to 10 years of follow-up. This study reviews a series of pancreas transplants at a single center to assess the donor and recipient characteristics for DCD pancreas transplant, and to compare clinical outcomes for these DCD and standard donors. Post-transplant clinical outcomes include post-transplant serum amylase and lipase, length of hospital stay, and short- and long-term graft survival.

Materials and Methods

Study population

The records of all pancreas transplants performed at a single center over a 13-year period from *** to *** were reviewed (606). There were 596 DBD pancreas transplants and 10 DCD pancreas transplants. A thrombolytic donor preflush protocol was introduced in July of 2011. In two patients, tissue plasminogen activator was infused as a thrombolytic during the first liter of donor flush as described elsewhere [16]. Follow up of the study population ranged from *** to ***. Pancreas procurement

In all DCD donors life support was withdrawn either in the operating room or nearby area. Heparin (300 IU/kg) was administered systematically at the time of withdrawal of life support according to the local donor hospital policies. After withdrawing life support, vital signs and oxygenation saturations were recorded. Organ procurement began 5 minutes after declaration of circulatory death by the declaring physician. The distal aorta was cannulated and flushed with preservation solution and the infrarenal inferior vena cava was vented for exsanguination. The average time from incision to aortic cannulation was less than 3 minutes. A midline sternotomy

was then made, the thoracic aorta was clamped, and the inferior vena cava was divided in the thoracic cavity. Ice-slush was placed on the abdominal organs and 3-4 L of cold HTK solution or University of Wisconsin was flushed through the aorta. Pancreas allografts were rapidly removed after completion of the aortic flush en bloc with the liver. The pancreata were then separated from the livers on the backtable[22]. Special care is required to avoid damage to vital structures during DCD donor organ procurement. Aberrant arterial vasculature is particularly vulnerable because dissection is performed in a cold field without blood flow or pulses evident to assist in identification of the vascular anatomy. All kidneys at our center are preserved with pulsatile perfusion until implantation.

Recipient operation

Backtable preparation of the DCD pancreas is identical to that of a standard donor and is described in detail elsewhere[23]. Briefly, a splenectomy is performed, the proximal donor duodenal staple line is oversewn with interrupted seromuscular stitches, the mesenteric staple is oversewn with a running horizontal matress stitch and the donor superior mesenteric and splenic arteries are reconstructed using a donor iliac artery Y graft.

The transplant operation was performed through a midline incision. The pancreas was routinely positioned with the tail toward the pelvis and the head and duodenum oriented superiorly in order to facilitate the enteric anastomosis. Systemic venous drainage was performed to the right common iliac vein or to the vena cava. Arterial perfusion of the allograft was routinely established from the right common iliac artery, although on rare occasions where this vessel was found to be diseased or had been the site for arterial anastomosis for a prior transplant, the inflow would be established either from the aorta or the left common iliac artery. All pancreas allografts were drained enterically using a stapled technique as described elsewhere[24]. In cases of SPK,

the allografts were positioned ipsilaterally as described elsewhere[25]. Total ischemia times were defined as the time from cardiac arrest of the donor patient to reperfusion in the recipient patient for DCD grafts. For DBD grafts, total ischemia times are defined as the time from cross clamping of the thoracic aorta until reperfusion in the recipient. This includes both warm and cold ischemia times.

The induction immunosuppression protocol consisted of five doses of rabbit antithymocyte globulin (rATG) (1 mg/kg/dose) and maintenance with tacrolimus (target trough 6-8 ng/ml), sirolimus (target trough 3-6 ng/ml). For PTA, mycophenolatemofetil (500 mg po bid) was also included as part of the maintenance regimen. Steroids were exclusively used as a premedication for rATG and were discontinued following induction in all recipients. As of October 2007, due to the higher incidence of chronic immunologic graft loss in the PTA population, we have also added a single dose of rituximab (150 mg/m^2) as well on post-operative day #1. All recipients received routine perioperative antibiotics, prophylaxis against cytomegalovirus (CMV) with oral valgancyclovir and prophylaxis against Pneumocystis jiroveci pneumonia with trimethoprim and sulfamethoxazole (Septra), unless contraindicated. Systemic anticoagulation was not routinely used unless the patient had a specific history of a coagulation disorder.

Post-transplant graft injury was assessed using measured laboratory values including peak serum amylase and lipase levels. Early graft loss was assessed by 7- and 90-day graft loss, while long term graft survival was assessed using the Kaplan-Meier method with Log-rank analysis (10-year).

Standard statistical testing was conducted with commercially available software. The comparisons were performed with the ANOVA for numerical data and the χ^2 test for categorical data. Survival rates were estimated with the Kaplan-Meier method. A p value less than 0.05 was considered to be significant. The retrospective analysis of data from the transplant research database at our center was reviewed and approved by the institutional review board of the Indiana University School of Medicine.

Results

Donor and recipient characteristics

Donor and recipient demographics are summarized in Table 1. Among the 10 DCD donors, 5 had their cause of death listed as anoxia, 4 were traumatic brain injury and 1 was a cerebrovascular accident. There were no statistically significant differences in donor demographics between the DBD and DCD donors including gender, race, age, BMI, and location of graft (local or not local).. There were also no significant differences between standard and DCD donors for recipient demographics including gender, race, age, and BMI. Of the 596 standard transplants, 54% were SPK, 19% were PAK, and 27% were PTA. Of the 10 DCD transplants, 6 were SPK and 4 were PTA. There were no PAK operations performed using DCD pancreata. The median total ischemia time for a DCD grafts was 5.4 hours, compared to 8.0 hours a standard donors (p = 0.15).

There was no difference in median peak serum amylase and lipase levels in the organ donor ($p = 0.68$ and 0.47), and no difference in the recipient post-transplant ($p = 1.00$ and 0.53) (Table 2). Similarly there was no difference in ength of stay, acute cellular rejection in the first year, early

graft loss (7- and 90-day), late graft loss (beyond 1 year), and patient survival. There were no cases of acute cellular rejection within the first year in the DCD group while there were 25 (4.2%) cases among standard donors ($p = 0.65$). There was no difference in early or late pancreas allograft survival with 100% graft survival in the DCD group up to 1-year post transplant and 92% survival in the standard group ($p = 0.46$). Of note, early and late renal allograft survival were also 100% up to 1-year post-transplant with no episodes of DGF. A Kaplan-Meier curve for graft survival shows similar survival for the two groups up to 10-years post-transplant (p=0.92) (Figure 1).

Discussion

In this study, we were able to excellent outcomes including alloggraft survival rate for a small number of carefully selected DCD donors compared to a large number of DBD donors out to a follow-up interval of 10 years. This result goes against conventional wisdom that DCD pancreata are inferior. With no significant differences between donor demographics, recipient demographics and transplant protocol and procedures leading to no difference in all clinically relevant post-transplant outcomes, this evidence supports the routine use of carefully selected DCD pancreas donors.

Although the use of other organs from DCD donors has increased in recent years, transplantation of the pancreas allograft from these donors has not yet gained widespread acceptance. In a US national survey among directors of pancreas transplant programs who have had experience with the use of DCD organs in pancreas transplantation, there was a general consensus that the donors should be otherwise ideal, meaning relatively young with a low BMI and hemodynamically stable. Half of the centers felt that these allografts could be used for either SPK or solitary

pancreas transplantation, 30% believed that these organs should be exclusively reserved for SPK and 20% said that these organs should be directed only to recipients of solitary pancreas transplants. A review of US data revealed that only 57 pancreas transplants from DCD donors were performed between 1993 and 2003 [17]. Only 13 US centers had transplanted pancreata from DCD donors as of 2006, representing 0.1% of all pancreas transplants. In this series, one- and five-yr pancreas graft survival rates in DCD donor recipients (85% and 74%, respectively) were comparable to pancreas graft survival rates in standard donor recipients (86% and 70%, respectively, p = NS), with a trend toward a higher thrombosis rate in DCD recipients (13% DCD vs. 6% standard, p = 0.06). SPKT recipients of DCD donor organs also had a higher rate of delayed renal allograft function (28% DCD vs. 8% standard, p < 0.05). The UW group has reported a large single-center experience with SPK transplants from DCD donors and showed similar five-yr pancreas graft survival rates in DCD and standard donor groups (92% DCD, 89% standard, p = 0.18), with no differences in patient survival, infection rates, thrombosis rates, and other functional outcomes [14]. Not unexpectedly, however, there was a higher incidence of kidney delayed graft function in the DCD donor recipients (24% DCD vs. 5% standard, p = 0.002).Similar results have also been shown by other investigators. Muthusamy et. al. in 2012 reported on 1009 PTs of which 875 were DBD and 134 were DCD. They found no significant difference in graft survival at 1 year for SPK, PAK, or PTA (*p* = 0.9, 0.6, and 0.6, respectively) and only a small increase in arterial thromboses in the DCD group. They did have a significant difference in donor characteristics; the median donor age between DBD and DCD was 9 years younger in the DCD group (*p* < .0001) and a BMI difference of 1 less in the DCD group as well (*p* = 0.04). [20] While the strength of this association is strong due to the large statistical power, Muthusamy et. al. recognizes that selecting younger, healthier patients for DCD can significantly

skew their results in favor of DCD outcomes. Quereshi et. al.in 2012 analyzed 60 PTs with 20 DCDs and 40 DBDs. They found no significant difference in graft survival at 18 months ($p = 0.181$) or donor and recipient demographics. [21]

The major limitation in this study is the number of subjects. However, unique to this patient cohort is the application of TPA flush in the donor procedure, which appears to be a safe practice if deemed necessary by one of the other organ procurement teams, and the routine application of pulsatile perfusion preservation of the renal allograft. Typically, pulsatile perfusion is not applied to SPK transplantation because of the relatively short ischemia time. As our program has been using pulsatile preservation for all renal allografts for decades, we have historically always included all of the renal allografts for SPKs as well. Of note, unlike other similar reports, we did not have a single instance of delayed renal allograft function in this cohort and will strongly advise this technique for DCD renal allograft.

Conclusions

These results support a growing body of evidence that DCD is equivocal to DBD in the right setting, and that this effect lasts beyond the 5-year period. The evidence argues for the routine use of carefully selected DCD pancreas donors as a means of increasing the availability of pancreata. There were no differences in graft function, post-operative complications, or early and late graft survival. Future studies should seek to identify prognostic scoring systems and risk factors for poor outcome in DCD PT that will increase the efficiency and the reliability of this practice.

Figures: Figure 1. 10-year Kaplan-Meier graft survival post pancreas transplant for DBD (n=10) and DCD donors (n=596)

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Donation after circulatory arrest in pancreas transplant

Table 1. Demographic data for 606 pancreas transplant patients with comparison of patients in which the deceased donor graft was procured using standard techniques or donation after circulatory death (DCD).

	Overall	Standard donor	Donation after circulatory death (DCD)	p-value
OVERALL	606	596 (98%)	10 (2%)	
RECIPIENT				
Gender: Male	56%	56%	60%	0.53
Race: White	91%	91%	100%	0.62
Age (median (years))	43	43	36	0.21
Body mass index (median)	24.9	25.0	23.7	0.24
DONOR				
Gender: Male	63%	63%	60%	0.54
Race: White	79%	78%	100%	0.26
Age (median (years))	24	24	21	0.69
Body mass index (median)	23.9	23.9	22.9	0.42
Donor cause of death				
Stroke	18%	18%	10%	0.11
Trauma	60%	60%	40%	
Anoxia / Other	22%	22%	50%	
Regional origin of graft				
Local	65%	64%	60%	0.57
Transplant data				
Transplant type				
Pancreas and kidney (n=328)	54%	54%	60%	0.26
Pancreas after kidney (n=116)	19%	20%	0%	
Pancreas alone (n=162)	27%	26%	40%	
Total ischemia (median (hours))	8.0	8.0	5.4	0.15

Table 2. Comparison of graft laboratory values and post-transplant outcomes by donor type, standard and donation after circulatory death (DCD).

	Overall	Standard donor	Donation after circulatory death (DCD)	p-value
OVERALL	606	596	10	
Donor laboratory value (median)				
Peak amylase	78	79	63	0.68
Peak lipase	31	32	23	0.47
Recipient laboratory values (median)				
Peak amylase	202	205	155	1.00
Peak lipase	154	154	113	0.53
Length of hospital stay (days, median)	7	7	7	0.56
Acute cellular rejection first year	25 (4.1%)	25 (4.2%)	0 (0%)	0.65
Survival				
7-day pancreas graft loss	20 (3.3%)	20 (3.3%)	0 (0%)	0.71
90-day pancreas graft loss	33 (5.4%)	33 (5.5%)	0 (0%)	0.57
1-year pancreas graft survival	93%	92%	100%	0.46
1-year patient survival	97%	97%	100%	0.74
Simultaneous pancreas-kidney (n=328)				
1-year pancreas graft survival	93%	93%	100%	0.66
1-year kidney graft survival	95%	95%	100%	0.74
1-year patient survival	97%	97%	100%	0.83

Donation after circulatory arrest in pancreas transplant

10-year Kaplan-meier graft survival post pancreas transplant in 606 patients