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Single Center Analysis of Mortality in 202 Consecutive Pancreas Transplants

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Abstract

Previous studies have questioned the safety of pancreas transplantation.

Methods:

We retrospectively reviewed survival outcomes in 202 consecutive pancreas transplants performed in 192 patients at our center.

Results:

From 11/01 to 3/13, we performed 162 simultaneous pancreas-kidney (SPK), 35 sequential pancreas after kidney (PAK), and 5 pancreas alone (PA) for a total of 40 solitary pancreas transplants (SPT). With a mean follow-up of 5.7 years in SPK versus 7.7 years in SPTs, overall patient survival was 86.5%; mortality rates were similar following SPK or SPT. Mortality rates were likewise similar following primary (13.6%) versus pancreas retransplants (6.25%, p=NS). No SPT recipients died early whereas the 1-, 3-, and 5-year mortality rates following SPK transplant were 4%, 9% and 12%, respectively ($p<0.05$). In SPK transplant patients who died, 15/21 (71%) experienced death with a functioning graft (DWFG) whereas 0/5 patients who died following SPT ($p=0.007$) experienced DWFG. Of the 26 total deaths, 15 were DWFGs, 3 died after kidney graft loss, 6 died after pancreas graft loss, and 2 following asynchronous kidney and pancreas graft loss. Three SPK transplant patients died early (within 5 months) of transplant secondary to technical issues. Of the remaining 23 deaths that occurred ≥6 months post-pancreas transplant (mean 53 months), 11 were cardiovascular, 7 infectious, 2 malignancy, and 3 miscellaneous causes. The proportion of patients age 50 or older at the time of transplant was higher in those who died (42%) compared to survivors (23%, p=0.05).

Conclusions:

Mortality rates following SPK, SPT and pancreas retransplantation are similar and correlate with older recipient age. Following SPK transplant, the mortality risk is constant and the most common mortality pattern is DWFGs whereas mortality following SPT occurs late and is heralded by graft loss. The most common causes of death are cardiovascular and infection regardless of pancreas transplant category.

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Introduction

Despite improvements in dialysis technology and overall health care including the management of diabetes mellitus, the presence of diabetes remains a significant predictor of mortality for patients on dialysis.[1] Even after making adjustments for confounding factors such as age and nutritional status, the 5-year survival of diabetic patients on dialysis is below 50%.[1] The poor 5-year survival of diabetic patients on dialysis makes kidney transplantation the preferred treatment for appropriately selected patients with end stage diabetic nephropathy.[2] However, the addition of a pancreas transplant remains controversial because of concerns over increased morbidities such as acute rejection, infection and technical complications that may result in higher mortality.[3,4] The purpose of this study was to review retrospectively our single center 11.5 year experience with the timing and causes of death following pancreas transplant in an attempt to identify trends and provide specific data for predicting subsequent outcomes.

Methods and Materials

Recipient Selection

Indications for pancreas transplantation were insulin-requiring diabetes with complications and the predicted ability to tolerate the operative procedure and manage the requisite immunosuppression and close follow-up irrespective of C-peptide production.[5] Selection criteria for solitary pancreas transplantation (SPT) were similar to simultaneous pancreas-kidney (SPK) transplantation except for renal function, in which the calculated abbreviated Modification of Diet in Renal Diseases (aMDRD) glomerular filtration rate (GFR) was >70 ml/min in pancreas alone (PA; native renal function) and >40 ml/min in sequential pancreas after kidney (PAK: renal allograft function) transplant recipients who were already receiving a calcineurin inhibitor. Donor selection was more stringent for SPT, including younger donors and a minimum of a 2-3 human leukocyte antigen (HLA) match. Selection criteria for SPK transplantation in "type 2" diabetes included patients <55 years of age with a body mass index (BMI) <30 kg/m^2, insulin-requiring for a minimum of 3 years with a total daily insulin requirement <1 u/kg/day, a fasting C-peptide level <10 ng/ml, absence of severe vascular disease or tobacco abuse, adequate cardiac function, and presence of "complicated" or hyperlabile diabetes.[5]

Technical Aspects

All patients were T- and B-cell negative by flow cytometry crossmatch. All pancreas transplants were initially approached as intent-to-treat with portal-enteric drainage (n=179) using an anterior approach to the superior mesenteric vein (SMV) and enteric exocrine drainage to the proximal ileum in the recipient (side to side duodeno-enterostomy, usually without a diverting Roux limb). In the absence of favorable SMV anatomy, pancreas transplantation with systemic venous (iliac vein) and enteric exocrine drainage (n=23) was performed.[5] Arterial inflow was usually based on the recipient's right common iliac artery after the pancreas dual artery blood supply was reconstructed with a donor common iliac bifurcation "Y" graft. Relative "contraindications" to portal venous drainage were a small SMV (<6mm in diameter); a deep, buried, or inaccessible SMV (usually associated with central obesity, particularly in recipients with a body mass index [BMI] >30 kg/m^2); a sclerotic or partially thrombosed SMV or history of venous thrombosis from a previous pancreas transplant with portal venous outflow; portal hypertension; or an arterial "Y" graft that would not reach a soft target either on the iliac artery or aorta. In patients (particularly male) with a high BMI, the SMV can be quite deep in the mesentery and the donor common iliac artery bifurcation "Y" graft might not be long enough to reach the recipient's iliac artery through a window in the distal ileal mesentery, even with the liberal use of a donor artery "extension" graft. In these cases, systemic venous and enteric drainage were performed to simplify the procedure. Of the first 121 SPK transplants, all but two were performed by transplanting the kidney to the left iliac vessels and the pancreas to the right common or external iliac artery through a midline intraperitoneal approach. However, since 7/30/10, nearly all SPK transplants were performed with ipsilateral placement of the kidney and pancreas to the right iliac vessels in order to reduce operating time and to preserve the left iliac vessels for future transplantation.

Anti-coagulation

In SPT and selected SPK transplant recipients, 2000 – 3000 units of intra-venous heparin (30 – 50 units/kg) were administered as a single dose during surgery prior to implantation of the pancreas and a heparin infusion was continued post-transplant (contin-uous infusion of 300 units/hour for 24 hours, then 400 units/hour for 24 hours, and then 500 units/hour until post-operative day 5) in the absence of bleeding.[5] Indications for intravenous heparin included SPT, preemptive SPK transplant, history of thrombophilia or clotting disorder in the recipient, small or diseased donor or recipient vessels, prolonged pancreas cold ischemia (>15 hours), extended donor criteria, or history of prior pancreas graft thrombosis.

Immunosuppression and Post-transplant Management

Patients received depleting antibody induction with either alemtuzumab (n=122) or alternate day rabbit anti-thymocyte globulin (rATG) (n=80, 1.5 mg/kg/dose, total 3 – 5 doses) in combination with tacrolimus, mycophenolate mofetil (MMF), and tapered corticosteroids or early steroid withdrawal.[5,6] Steroids were completely stopped on post-operative day #5 unless the patient was identified as "high immunological risk" defined by the presence of delayed (kidney) graft function, retransplantation, African American (AA) patient <40 years of age, allosensitization (pre-transplant panel reactive antibody [PRA] level >20%), or PA transplant. Since 2009, all pancreas transplant recipients at our center (n=74) have received alemtuzumab induction with tacrolimus, MMF, and either early steroid elimination or rapid prednisone taper (dose reduction to 5 mg/day by 2 months following pancreas transplantation if determined to be high immunological risk).[5,6] All patients received anti-infective prophylaxis with cefazolin for surgical site prophylaxis, fluconazole, valganciclovir, and trimethoprim-sulfamethoxazole. Anti-platelet therapy, consisting of oral aspirin (81 mg/day) was administered to all patients. Most patients were discharged from the hospital after placement of a tunneled central venous catheter and received intravenous fluid and electrolyte supplementation at home for a variable period of time. Treatment of hypertension, hyperlipidemia, anemia, and other medical conditions was initiated as indicated, aiming to maintain the blood pressure <140/90 mm Hg, fasting serum cholesterol <200 mg/dl, and hematocrit >27%.

Statistical Analysis

Data were compiled from both pros-pective and retrospective databases, with confirmation by medical record review in accordance with local Institutional Review Board guidelines and approval. For categorical variables, the chi-square test was applied, and Fisher's exact test was used when data were sparse. Categorical data were summarized as proportions and percentages and continuous data were summarized as means and standard deviations. Cumulative survival curves were estimated by Kaplan-Meier analysis. A two-tailed p-value of <0.05 was considered to be significant. Based on limitations in study design and the lack of significance for outcome variables in univariate analysis, we refrained from performing a multivariate analysis and present our findings mainly in a descriptive fashion.

Results

From 11/1/01 through 3/1/13, 202 consecutive pancreas transplants were performed in 192 patients, including 162 SPK, 35 sequential PAK, and 5 PA (40 SPTs). Demographic and clinical characteristics of the patient population are displayed in Table 1. Demographic characteristics were mostly comparable; however, the SPT group had younger donors, shorter waiting time, fewer HLA mismatches, fewer AA recipients, but more retransplants (all p<0.05). A total of 186 pancreas transplants (92%) were primary and 16 retransplants. With a mean follow-up of 5.5 years in SPK versus 7.5 years in SPT (range 0.5-12 years, 140 patients had a minimum follow-up of 5+ years), mortality was similar following either SPK (13.6%) or SPT (13.2%). Five year actuarial patient survival rates are shown in Figure 1 (p=NS). In addition, overall kidney (74% SPK versus 80% SPT) and pancreas graft survival (both 65%) rates were comparable. Mortality rates were likewise similar following primary (13.6%) versus pancreas retransplant (6.25%, p=NS). No SPT recipients died early whereas the 1-, 3-, and 5-year mortality rates following SPK transplant were 4%, 9% and 12%, respectively (p<0.05). In SPK transplant patients who died, 15/21 (71%) experienced death with a functioning graft (DWFG) whereas 0/5 patients who died following SPT (p=0.007) experienced DWFG (4 had prior kidney graft loss and 3 had prior pancreas graft loss).

A total of 39 pancreas transplants (36 SPK, 2 PAK, and 1 PA) were performed in AA recipients and the remaining 163 in non-AA recipients (161 Caucasian, 1 Asian, and 1 Hispanic). In addition, of the 162 SPK transplants, 132 were performed in patients with absent or low C-peptide levels (<2.0 ng/ml, including 21 with measurable C-peptide) and 30 in patients with C-peptide levels ≥2.0 ng/ml (mean C-peptide level 5.7 ng/ml, range 2.1-12.4). Mortality rates were similar according to recipient ethnicity (11.3% AA versus 13.8% non-AA), C-peptide positivity (10% C-peptide positive versus 14.5% C-peptide negative), transplant technique (14% portal-enteric versus 13% systemic-enteric), and method of antibody induction (15% alemtuzumab versus 12% rATG; all p=NS).

Of the 26 total deaths, 15 were DWFGs, 3 died after kidney graft loss, 6 died after pancreas graft loss, and 2 following asynchronous kidney and pancreas graft losses. In the absence of either kidney or pancreas retransplantation, mortality rates following isolated kidney, isolated pancreas, and pancreas-kidney graft losses were 33%, 24%, and 17%, respectively (p=NS). However, 6 patients underwent successful kidney retransplantation and 11 patients underwent successful pancreas retransplantation; mortality following either kidney or pancreas retransplantation or both was 5%. Three SPK transplant patients died early (within 5 months) of infection secondary to technical issues. Of the remaining 23 deaths that occurred ≥6 months following pancreas transplantation (mean 53 months), 11 were cardiovascular, 7 infectious, 2 malignancy (one lung, one native pancreas cancer), and 3 miscellaneous causes (one motor vehicle wreck, one drug overdose, one cirrhosis). The proportion of patients aged 50 or older at the time of pancreas transplant was higher in those who died (42%) compared to survivors (23%, p=0.05).

Discussion

Previous studies have questioned the safety of pancreas transplantation because diabetes is an independent risk factor for coronary artery disease and cardiac death.[3,4,7,8] However, according to International Pancreas Transplant Registry data, for recipients of primary deceased donor pancreas transplants in the United States, one-year patient survival rates are more than 95% in all 3 categories; unadjusted five-year patient survival rates are 87% in SPK, 83% in PAK, and 89% in PA transplant recipients; and more than 70% of patients are alive at ten years post-transplant.[9] Previous reports have also identified recipient age above 45 years, pre-existing heart disease, retransplantation and technical graft failure as independent risk factors for mortality following pancreas transplant.[9] However, many diabetics referred for pancreas transplantation have heart disease; those with occult, uncorrectable or irreversible disease appear to fare less well and one might assume that late cardiac mortality following pancreas transplantation is inevitable in some patients irrespective of the effects of transplantation.

In our series, the overall mortality rate was 13.5% and was not influenced by type of transplant, transplant number, technique of transplant, depleting antibody induction agent, recipient ethnicity, or presence of C-peptide pretransplant. Cardiovascular and infectious causes accounted for 81% of the deaths. Three deaths occurred early and were associated with surgical complications and infection, whereas cardiovascular deaths usually occurred late and were related to older recipient age or preceded by kidney or pancreas graft loss. The mortality rate was low albeit constant over time following SPK transplant whereas no mortality occurred in the first 4.5 years following SPT. Unique aspects of our experience include relatively large numbers of AA recipients as well as patients with detectable C-peptide levels pretransplant; both of which suggest a "Type 2" diabetes phenotype. In addition, we report herein a large number of patients receiving pancreas transplantation with portal-enteric drainage and depleting antibody induction. However, none of these factors appeared to influence mortality rates.

In summary, mortality rates following SPK, SPT and pancreas retransplantation were similar and correlated with older recipient age. Following SPK transplant, the most common mortality pattern was DWFGs and the mortality risk was constant whereas mortality following PAK or PA transplant was heralded by either kidney or pancreas graft loss or both and occurred late. The most common causes of death were cardiovascular and infection regardless of pancreas transplant category. Kidney or pancreas graft losses were both predictive of subsequent mortality whereas retransplantation of either organ appeared to reduce mortality. Future strategies aimed at reducing mortality following pancreas transplantation should emphasize appropriate recipient selection, cardiovascular risk, and target prevention of operative complications.

Authors

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Mean ± SD	SPK 162 in 161 patients*	SPT 40 in 38 patients*	Total 202 in 192 patients*
Donor age (years)	27.3 ± 10.6	22 ± 7.6	26.2 ± 9.2
Donor BMI (kg/m^2)	23.9 ± 1.4	23.5 ± 6.8	23.8 ± 3.6
Donation after cardiac death (DCD) donors	5 (3.1%)	0	5 (2.5%)
Cold ischemia time (hours)	16.2 ± 7.4	14.8 ± 3.8	15.9 ± 5.7
HLA-mismatch	4.5 ± 1.2	2.7 ± 1.5	4.1 ± 1.3
PRA >10%	27 (16.7%)	8 (20%)	35 (17.3%)
CMV Donor+/Recipient-	45 (27.8%)	11 (27.5%)	56 (27.7%)
Retransplant	2 (1.2%)	14 (35%)	16 (7.9%)
Portal-enteric technique	147 (90.7%)	32 (80%)	179 (88.6%)
Recipient age (years)	42.7 ± 11.3	42.2 ± 8.7	42.6 ± 10.1
Recipient gender: Male	94 (58.4%)	19 (50%)	110 (57.3%)
Recipient: African American	36 (22.5%)	3 (7.9%)	38 (19.8%)
Recipient weight (kg)	71.1 ± 13.5	70.7 ± 12.8	71.0 ± 13.2
Dialysis history: Hemodialysis Peritoneal Dialysis None (preemptive)	82 (50.9%) 42 (26.1%) 37 (23%)	NA	82 (42.7%) 42 (21.9%) 36 (18.75%)
Duration of pretransplant diabetes (years)	25.3 ± 9.8	26.7 ± 7.7	25.6 ± 8.9
Waiting Time (months)	10.1 ± 6.3	5.8 ± 7.2	9.2 ± 6.6
Alemtuzumab induction	100 (61.7%)	22 (55%)	122 (60.4%)
C-peptide positive	30 (18.6%)	0	30 (15.6%)
Mortality	21 (13.6%)	5 (13.2%)	26 (13.5%)
Follow-up (months)	68.7 ± 96	92.1 ± 37	73.2 ± 54
Death in first 4 years post-transplant	10 (6.2%)	0	10 (5.2%)
Death with functioning grafts	15 (9.3%)	0	15 (7.8%)
Patients aged 50 or older	42 (26.1%)	8 (21.1%)	49 (25.5%)

Table 1: Demographic and Clinical Features of Patient Population

*One patient had 2 SPK transplants, two had 2 SPTs, and seven had SPK followed by SPT at our center.