A 9-Year Experience With 126 Pancreas Transplants With Portal Enteric Drainage

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Hypothesis: A novel technique of pancreas transplantation (PTX) with portal venous delivery of insulin and enteric exocrine drainage (portal enteric) was developed at our center to improve the PTX procedure.

Design: Case series.

Setting: Single-center experience at a university hospital.

Patients and Intervention: From October 1990 through December 1999, we performed 126 PTXs with portal enteric drainage, including 90 simultaneous kidney PTXs (SKPT) and 36 solitary PTXs (18 sequential PTXs after kidney transplantation and 18 PTXs alone).

Main Outcome Measures: Patient and graft survival rates; medical and surgical morbidity. Three groups, representing 3 eras of immunosuppression, were compared. Thirty patients underwent SKPT with muromonab-CD3 induction and cyclosporine-based therapy in era 1 (October 1990 through June 1995); 42 SKPTs received tacrolimus and mycophenolate mofetil-based immunosuppression without antibody induction in era 2 (July 1995 through May 1998); and 18 SKPTs were performed in era 3 (June 1998 through December 1999) with either basiliximab or daclizumab induction.

Results: One-year patient survival rates after SKPT were 77% in era 1, 93% in era 2, and 100% in era 3 (P = .03). The 1-year kidney graft survival rates were 77% in era 1, 93% in era 2, and 94% in era 3 (P = .08). The 1-year pancreas graft survival rates after SKPT were 60% in era 1, 83% in era 2, and 83% in era 3 (P = .06). The incidences of rejection (63% vs 33% vs 39%; P < .001) and thrombosis (20% vs 7% vs 6%; P < .001) were decreased in eras 2 and 3.

Conclusion: Simultaneous kidney PTXs with portal enteric drainage can be performed with improved outcomes.

METHODS

The PTX program at the University of Tennessee (Memphis) was started in 1989 (Figure 1). The first SKPT with PE drainage was performed in October 1990, and this patient continues to demonstrate excellent dual allograft function more than 10 years later. During the 9 years that followed, we performed 126 PTXs with PE drainage (Figure 2), including 90 SKPTs and 36 solitary PTXs (18 PAKT, 18 PTXs alone). This study represents a case series and our collective experience with the PE technique.5-10

ORGAN PROCUREMENT, PRESERVATION, AND PREPARATION

The pancreas and/or kidneys were procured from heartbeating cadaveric donors in conjunction with multiple organ retrieval using standardized techniques.11 UW solution (Viaspan; Dupont Pharmaceuticals, Atlanta, Ga) was used for both in situ flush and storage of all organs under cold storage conditions. Whole-organ pancreaticoduodenal procurement was performed by an en bloc technique.11 Cold ischemia was kept to a minimum and pancreas preservation times were less than 24 hours in all cases and less than 12 hours in about one third of cases.11 Prior to transplantation, the pancreas was reconstituted with a donor iliac artery bifurcation Y-graft to the splenic and superior mesenteric arteries.10,13 The PE procedure requires that the arterial bifurcation graft be constructed with enough length for subsequent arterIALIZation. The donor portal vein was mobilized and dissected back to the splenic and superior mesenteric venous confluence without the need for a venous extension graft. The proximal duodenal staple line (just distal to the pylorus) was inverted with interrupted sutures, and the distal duodenal closure incorporated the third order iliac artery bifurcation graft is brought through a window made in the distal ileal mesentery and anastomosed end-to-side to the right common iliac artery. The transplanted duodenum is anastomosed to a diverting Roux-en Y limb of the recipient jejunum. Spleenectomy is performed after revascularization, and an attempt is made to anchor the tail of the pancreas to the anterior abdominal wall with interrupted sutures. These anchoring sutures permit subsequent percutaneous, ultrasound-guided pancreas allograft biopsies to be performed as needed.14

IMMunosUPPRESSIVE ERAS

Figure 4 summarizes the immunosuppressive therapy performed in each era. From October 1990 through June 1995 (era 1), 30 SKPTs with PE drainage were performed at our center with quadruple therapy consisting of muromonab-CD3 induction in combination with cyclosporine (Sandimmune; Sandoz Pharmaceuticals Corp, Hanover, NJ), prednisone, and azathioprine sodium.6 The cyclosporine dose was titrated to achieve a target 12-hour trough level of greater than 300 ng/mL for the first 3 months after transplantation and greater than 200 ng/mL thereafter. The azathio-prine dosage was 1 to 2 mg/kg per day. The prednisonone dose was tapered to achieve a dose of 10 mg/d by 1 year and 5 mg/d by 2 years after transplantation.

From July 1995 through May 1998 (era 2), 42 SKPTs and 23 solitary PTXs (11 PAKTs, 12 PTXs alone) received tacrolimus (TAC), prednisone, and mycophenolate mofetil (MMF) triple therapy without antibody induction.15,16 The tacrolimus dose was titrated to a 12-hour trough level of 15 to 25 ng/mL for the first 3 months after transplantation. After 3 months, TAC blood levels were maintained at 10 to 15 ng/mL. Oral MMF therapy was started immediately after transplantation at 2 to 3 g/d in 2 to 4 divided doses. The MMF dose was reduced in patients with gastrointestinal intolerance (nausea, vomiting, diarrhea) or when the complete white blood cell count was less than 3.0 × 10^9. Mycophenolate mofetil therapy was discontinued temporarily in patients with active cytomegalovirus infection or septicemia, or when the complete white blood cell count was less than 2.0 × 10^9; it was restarted later at a reduced dose. The prednisone dose was gradually tapered to achieve a dose of 3 mg/d at 1 year. From June 1998 through December 1999 (era 3), 18 SKPTs and 13 solitary PTXs (7 PAKTs, 6 PTXs alone) received TAC, MMF, and prednisonone immunosuppression with 126 PTXs with PE drainage spanning different immunosuppressive eras.

RESULTS

The PE group included 69 men and 57 women with a mean age of 39 years (Table 1). The mean duration of pretransplant diabetes was 24 years (range, 8-50 years). Most recipients were white, although 15 recipients (12%) were African American. A total of 13 patients (10%) un-
derwent pancreas retransplantation with the PE technique. Most patients had poor HLA matching (mean, 1.4; range, 0-5), and the mean pancreas cold ischemia was 13 hours (range, 6-23 hours).

Thirty patients underwent SKPT in era 1 and were compared with 42 SKPTs performed in era 2 and 18 in era 3. We also compared 23 solitary PTXs (11 PAKTs, 12 PTXs alone) performed in era 2 with 13 (7 PAKTs, 6 PTXs alone) performed in era 3 (Figure 2). One-year patient survival rates after SKPT were 77% in era 1, 93% in era 2, and 100% in era 3 ($P = .03$). The 1-year kidney graft survival rates were 77%, 93%, and 94%, respectively ($P = .08$). The 1-year pancreas graft survival rates after SKPT were 60%, 83%, and 83% ($P = .06$) (Figure 6). The most common causes of kidney graft loss were death with function and chronic rejection (Table 2). The overall incidence of kidney graft loss decreased from 56% in era 1 to 23% in era 2 to 11% in era 3 ($P < .001$). The most common causes of pancreas graft loss were thrombosis, death with function, chronic rejection, and infection

with or without either basiliximab or daclizumab antibody induction (Figure 5). Half of the SKPT and all of the solitary PTX recipients received either basiliximab (20 mg intravenously on days 0 and 4) or daclizumab (1 mg/kg on day 0 and then at 2-week intervals for a total of 5 doses) as induction therapy. The diagnosis of rejection was based on clinical criteria, renal allograft dysfunction, serum amylase, lipase, and glucose levels, a change in the slope of glucose disappearance, and renal or pancreas allograft histopathology. Renal allograft rejection was suggested by an unexplained rise in serum creatinine of 0.3 mg/dL (26.52 μmol/L) or greater confirmed by ultrasound-guided percutaneous biopsy. Pancreas allograft rejection was suggested by an unexplained elevation in serum amylase, lipase, or glucose, and confirmed by ultrasound-guided percutaneous biopsy. The severity of rejection was defined according to the Banff criteria for kidney biopsies and by a modification of the Maryland classification of allograft rejection for pancreas biopsies. Mild renal allograft rejection was treated with intravenous methylprednisolone, 500 to 1000 mg/d, for 3 days. Antilymphocyte therapy with muromonab-CD3, antithymocyte gamma globulin (Upjohn Laboratories, Kalamazoo, Mich), or thymoglobulin for 5 to 10 days was used as the initial treatment for moderate or severe renal allograft rejection or for any pancreas allograft rejection. Steroid-resistant mild renal allograft rejection was also treated with antilymphocyte therapy.

**PERIOPERATIVE MANAGEMENT**

Perioperative antibiotic prophylaxis consisted of a preoperative, intraoperative, and 3 postoperative doses of cefazolin sodium (1 g intravenously). All patients received single-strength sulfamethoxazole/trimethoprim sulfate, 1 tablet per day, for 6 to 12 months as prophylaxis for *Pneumocystis pneumonia*. Patients who were allergic to sulfa medications received inhaled pentamidine therapy. Antifungal prophylaxis consisted of either oral nystatin (swish and swallow 5 mL, 4 times daily) or oral fluconazole, 200 mg/d, for 2 to 3 months. Antiviral prophylaxis consisted of either oral acyclovir sodium for 3 months (era 1), intravenous ganciclovir sodium followed by oral acyclovir for 3 months (era 2), or intravenous ganciclovir (2.5-5 mg/kg twice daily) during the initial hospitalization, followed by oral ganciclovir (1 g 3 times daily) for 3 months (era 3). Patients were monitored in the intensive care unit for 24 to 36 hours before being transferred to the transplant unit. Nasogastric tube decompression was maintained for 2 to 3 days, closed-suction drainage for 3 to 5 days, and urethral catheter drainage for 3 to 7 days. Antiplatelet therapy consisting of oral aspirin (81 mg/d) was administered to all patients. In addition, 2000 to 3000 U of intravenous heparin sodium was administered as a single dose during surgery before implantation of the pancreas. In most cases, heparin prophylaxis was continued after surgery (5000 U subcutaneously twice daily) for 3 to 5 days. Oral warfarin sodium in a single dose of 1 mg/d was administered to patients requiring prolonged vascular access or those with subsequent placement of a permanent central venous catheter. Several management protocols evolved over time, including (1) donor selection restricted to ideal situations, particularly in solitary PTX; (2) protective cytomegalovirus-matching (seronegative donor organs transplanted into a seronegative recipient); (3) minimizing cold ischemia, particularly for nonideal donors; (4) routine anticoagulation and HLA matching, especially in retransplants and solitary PTXs; (5) routine ganciclovir and fluconazole prophylaxis; and (6) surveillance pancreas biopsy monitoring (particularly for solitary PTX recipients).

**POSTOPERATIVE MONITORING**

After transplantation, duplex ultrasonography of the pancreas and/or the kidney was performed on the first postoperative day and whenever clinically indicated. Patients were serially monitored for daily fasting serum glucose, amylase, and lipase levels, renal profiles, cyclosporine or TAC levels, and complete blood cell counts. Metabolic control and hormonal profiles were assessed by intravenous glucose tolerance testing, fasting and stimulated C-peptide levels, lipid profiles, and glycosylated hemoglobin levels. Cytomegalovirus infection was defined as a positive blood culture, antigenemia, or an immunoglobulin M titer. Invasive cytomegalovirus infection was defined as symptomatic cytomegalovirus infection or histologic evidence of tissue invasion. Treatment consisted of intravenous ganciclovir for 2 to 4 weeks and a reduction in immunosuppression. Oral acyclovir or ganciclovir was given for a variable period after treatment of a documented cytomegalovirus infection. Other infections were recorded, with major infection defined as the need for hospitalization for diagnosis or treatment.

**STATISTICAL ANALYSIS**

Minimum follow-up was 11 months (mean, 4-6 years). Renal allograft loss was defined as death with function, transplant nephrectomy, return to dialysis, or return to the pretransplant serum creatinine level. Pancreas graft loss was defined as death with function, transplant pancreatectomy, or the need for daily insulin therapy.

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The overall incidence of pancreas graft loss decreased from 60% in era 1 to 31% in era 2 to 22% in era 3 (P < .001).

The incidences of rejection in eras 1, 2, and 3 (63% vs 33% vs 39%, respectively; P < .001) and major infection (60% vs 43% vs 44%; P = .14) after SKPT were decreased in consecutive eras (Figure 7). The rates of thrombosis (20% vs 7% vs 6%; P < .001) and early relaparotomy (47% vs 31% vs 33%; P = .15) after SKPT were also decreased in consecutive eras (Figure 8).

The 1-year patient survival rates after solitary PTX were 100% in eras 2 and 3, while the corresponding pancreas graft survival rates were 61% and 69%, respectively (Table 3). The most common causes of graft loss after solitary PTX were thrombosis and chronic rejection. The overall incidence of pancreas graft loss after solitary PTX decreased from 70% in era 2 to 31% in era 3 (P = .02). The rates of acute rejection (57% vs 38%), major infection (35% vs 31%), thrombosis (22% vs 15%), and relaparotomy (43% vs 38%) after solitary PTX were all slightly improved in era 3 compared with era 2 (P = .36).

The history of clinical PTX largely revolves around the development and application of various surgical techniques. As surgical techniques evolve, an increasing number of PTXs are performed with enteric drainage (about 60% of cases in 1999). However, the proportion of cases with enteric exocrine drainage coupled with portal venous delivery of insulin has remained low and represents only 15% to 20% of enteric-drained PTXs. In a

**COMMENT**
recent survey of surgical techniques among PTX centers, 7 reported experience with the PE technique, of which 5 used a diverting Roux limb.30 The International Pancreas Transplant Registry analysis of PTXs performed between 1996 and 1999 reported that the 1-year pancreas graft survival rates were similar for PE and SE drainage (83% and 84%, respectively).1,2 We have previously reported our initial experience with PE drainage, including both retrospective and prospective comparisons with control groups of patients who underwent SKPT with either SB or SE drainage.3-10

Experience with PTX using portal venous delivery of insulin dates back to the mid 1980s. Initial attempts employed segmental PTX with either gastric,30 pyelic,31 or jejunal32,33 drainage. Whole-organ PTX using the PE technique was first described clinically by our group in 19923 and was based on experimental work by Shokouhi-Amiri et al34-36 in a porcine model. This new technique employed a tributary of the superior mesenteric vein to reestablish portal venous drainage and differed substantially from other initial reports of whole-organ PTX with portal venous drainage. In 1990, Muhlbacher et al37 described a technique involving an end-to-side anastomosis between the distal splenic vein of the donor and the recipient’s portal vein in combination with bladder drainage. In 1992, Rosenlof et al38 applied Calne’s30 original technique to whole organ PTX using an end-to-side anastomosis between the donor portal vein and recipient splenic vein coupled with enteric drainage. In each of these other series, however, the procedure was not widely applied because of technical problems associated with the vascular reconstruction.39

In 1993, our group reported that PTX with PE drainage with Roux limb diversion not only achieved acceptable metabolic control and eliminated hyperinsulinemia but was also associated with reduced postoperative complications.5 In 1995, we compared 19 patients un-
In 1995, Newell et al reported their initial experience with a similar PE technique in 12 SKPT recipients compared with a retrospective matched control group of 12 SKPT patients with SB drainage. Six-month patient and graft survival rates were comparable, and the PE group had less acidosis, dehydration, hematuria, rejection, and need for enteric conversion. There were no differences in technical complications, and renal and pancreas allograft functions were similar. In 1996, Newell et al presented a 12-month follow-up on the same group of patients undergoing SKPT with PE drainage with a retrospective control group of 28 patients receiving SKPT with the conventional SB technique. Actuarial patient and graft survival rates at 1 and 3 years were no different between the 2 groups. Metabolic and urologic complications and urinary tract infections were more common in the SB group. Metabolic control was comparable between groups, and peripheral hyperinsulinemia did not occur in patients with PE drainage.

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using a Roux limb. Kidney and pancreas graft survival rates were both 90%, with 1 graft loss caused by thrombosis. Buell et al also updated the Busing et al experience, including 16 SKPTs with PE drainage without a Roux limb. This group also reported good initial results with the PE technique in the absence of a diverting Roux limb.

In 1999, Reddy et al reported a reduction in the surgical complication rate after PTX with PE drainage that was attributed to increased experience with the technique. Also in 1999, Stratta et al reported that the incidence of allograft pancreatocutaneous fistulae was not influenced by the surgical technique of implantation.

In 1999, Philippou et al compared their initial experience with 66 PTXs using PE drainage compared with 183 PTXs using SE drainage. Graft survival rates of recipients of SKPTs, PAKTs, and PTXs alone were similar. However, when stratified for HLA matching, the incidence of rejection was lower in patients with PE drainage. In a follow-up report in 2000, Philippou et al compared 117 solitary PTXs using PE drainage with 70 using SE drainage. The authors noted not only an improvement in the pancreas graft survival rate, but also a decrease in the incidence and severity of rejection in patients with PE drainage. The authors concluded that PE drainage may be associated with an immunologic advantage.

In 2000, Petrillo et al reported a prospective study of 34 SKPT recipients randomized to either receive SE or PE drainage with a Roux limb. Patient and graft survival rates and morbidity were similar between groups. In 2001, Stratta et al prospectively compared 44 consecutive SKPTs performed with either SE (n=22) or PE (n=22) drainage. Again, patient and graft survival rates as well as medical and surgical morbidity were comparable between groups. Both of these studies concluded that whole organ PTX with a standardized technique of PE drainage can be performed with short-term results comparable to the conventional technique of SE drainage.

In 2000, Stratta et al prospectively alternated 32 consecutive PTXs to either SB (n=16) or PE (n=16) drainage with standardized immunosuppression. Patient and graft survival rates and operative complications were comparable between groups after either SKPT or solitary PTX. There were no graft losses either to immunologic or infectious complications in either group, but the incidence of acute rejection was slightly higher in the SB group (SB, 44% vs PE, 31%; P=.24). Moreover, the SB group was characterized by a slight increase in the number of readmissions, urinary tract infections, urologic complications, metabolic acidosis, and dehydration. Also in 2000, Cattral et al prospectively studied 20 SKPTs with SB drainage followed by a sequential cohort of 20 consecutive SKPTs with PE drainage. One-year patient and graft survival rates were similar between groups. However, medical morbidity, cytomegalovirus infections, and acute rejection were more common in the SB group. Zibari et al reported their initial experience with 17 SKPTs with PE drainage and a Roux-en-Y venting jejunostomy to monitor for rejection and prevent anastomotic leak. Patient, kidney, and pancreas graft survival rates were 100%, 100%, and 94%, respectively, after a mean follow-up of 16 months. In each of these studies, the authors concluded that SKPT with PE drainage can be performed with excellent short-term outcomes and minimal morbidity.

Our study reports the chronology of our experience with PE drainage spanning different immunosuppressive eras. The major findings were that (1) inferior outcomes occurred after SKPT in era 1; (2) the results of SKPT in eras 2 and 3 were remarkably similar; and (3) the results of solitary PTX were slightly improved in era 3 compared with era 2. With regard to SKPT, patient and kidney graft survival rates were nearly identical in each era, reflecting the fact that death with function was the most common cause of kidney graft loss. In the first year after SKPT, kidney graft loss owing to either immunologic or technical complications was uncommon. When censoring for death with function, the differences in kidney graft survival rates between the eras were eliminated. In contrast, censoring for death with a functioning graft did not eliminate the differences in pancreas graft survival rates between the eras. In the first year after SKPT, pancreas graft loss was usually caused by either thrombosis or infection. Pancreas graft loss caused by rejection was uncommon. However, in patients with functioning grafts, the incidences of either acute rejection or thrombosis were significantly lower in eras 2 and 3 compared with era 1. Although era 1 may represent a “learning curve” effect, there is no question that the switch from cyclosporine (era 1) to TAC-based immunosuppression (eras 2 and 3) had a dramatic effect on outcomes. Surprisingly, the addition of either basiliximab or daclizumab to TAC/MMF therapy (era 3) did not have any discernible effect on outcomes after SKPT. The potent immunosuppressive state achieved with the combination of TAC, MMF, and steroids may have overshadowed any potential benefits of monoclonal antibodies directed at the interleukin-2 receptor. Coincident with a decrease in the incidence of acute rejection achieved with TAC/MMF therapy, we also noted a reduction in the risk of thrombosis after SKPT with PE drainage. It has been suggested that many cases of pancreas allograft thrombosis are caused by immunologic rather than technical factors. Other changes that occurred over time and possibly influenced the risk of thrombosis included restricted donor selection, protective cytomegalovirus matching, minimizing cold ischemia, and routine perioperative anticoagulation.

With regard to solitary PTX, modest improvements were noted in all outcome parameters measured in era 3 compared with era 2. However, none of these differences were statistically significant because of small numbers. In contrast to SKPT, death with a functioning graft was not an early consideration, since the 1-year patient survival rates were 100% in both eras. The decrease in the rates of acute rejection and thrombosis occurring in era 3 are clinically significant, and might reach statistical significance with larger numbers. Further changes that occurred in management protocols that might have contributed to improved outcomes after solitary PTX in era 3 included routine anticoagula-
tion, HLA matching, and surveillance pancreas biopsy monitoring.

In summary, this overall experience demonstrates that SKPT and solitary PTX with PE drainage can be performed with improved outcomes. Increasing experience with the PE technique coupled with advances in immunosuppression are associated with (1) increasing patient, kidney, and pancreas graft survival rates; (2) less medical morbidity with a decreasing incidence of acute rejection and major infections; and (3) reduced surgical complications including decreasing rates of thrombosis and relaparotomy. The PE technique does not seem to incur any additional or unique risks and can be performed yielding results comparable with the other standard techniques of PTX. We believe that this technique should be included in the repertoire of PTX, because it offers potential physiologic, metabolic, and immunologic advantages compared with the other techniques currently available.

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