

Original Article

Pancreas Transplantation in Shiraz Organ Transplant Center; The First Iranian Experience

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Background: Pancreas transplantation is the treatment of choice for selected patients with type 1 diabetes mellitus. We reviewed our first 40 patients who underwent pancreas transplantation in Shiraz Organ Transplant Center.

Methods: Between April 2006 and April 2008, we performed pancreas transplantation on 40 recipients. The operation included portal venous drainage and exocrine enteric drainage. Immunosuppressive therapy included prednisolone, tacrolimus, and mycophenolate mofetil. Ganciclovir was administered as prophylaxis for cytomegalovirus. Peri-operative and regular follow up data on survival and complication were gathered and analyzed.

Results: The mean follow-up was 10.1 ± 6.5 months (range: 1 – 24 months). Mean age of donors and recipients was 23.6 ± 8.2 and 32.30 ± 8.9 years, respectively. The mean pretransplant insulin consumption was 43.75 ± 17.4 IU. Fasting blood glucose before transplantation was 275.5 ± 72.3 mg/dL that decreased to 95.6 ± 7.01 at six months follow-up ($P < 0.001$). Complications were as follows: re-exploration ($n=9$), gastrointestinal complications ($n=10$), acute rejection episodes ($n=12$), and chronic rejection ($n=4$). We lost one patient due to diffuse cytomegalovirus and aspergillus infection three months after the operation with a functioning graft. Overall graft survival was 84.9% and patient survival 97.5%.

Conclusion: Good patient and graft survival in these series encouraged us to continue the program with all its difficulties.

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Keywords: Diabetes mellitus • end-stage renal failure • pancreas transplantation

Introduction

Pancreas transplantation (PTx) was performed for the first time in human in 1966,^{1,2} but it was in the 1980s, with advances in surgical technique and introduction of cyclosporine for immunosuppression, that the success rates became acceptable. PTx from

deceased donors has become a widely accepted therapeutic option for certain groups of insulin-dependent diabetic patients. The aim of performing this procedure is to provide the diabetic patients with a euglycemic state without the need for regular blood glucose monitoring and insulin injections. It also resolves uremic state when combined with kidney transplantation and has the potential to halt the disease progression associated with chronic hyperglycemia.

Shiraz Organ Transplant Center is a leading center for organ transplantation and the largest center for liver transplantation in Iran. We also performed PTx for the first time in Iran in April 2006. Here, we report the results of our experience

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with PTx in the first two years.

Materials and Methods

Between April 2006 and April 2008, we performed PTx on 40 recipients, 23 simultaneous kidney-pancreas transplantations (SPK), 14 pancreas transplantations alone (PTA), and three pancreas after kidney (PAK) transplantations. The operation, its indication, and possible complications were described to all the recipients in detail and informed consent was obtained.

The selection criteria for consideration of each type of operation were as follows: PTA for patients with normal renal function and brittle type 1 diabetes (hypoglycemic unawareness, difficulty in diabetic control with insulin injection, and frequent acute metabolic complications); SPK for diabetic patients <50 years who are concomitantly candidates for renal transplantation; PAK for previously renal transplantation diabetic cases with normal functioning graft after one year. Data were gathered from hospital medical charts before and after the transplantation, during postoperative hospital stay, and at regular follow-ups.

Recipients were known cases of insulin-dependent diabetes mellitus less than fifty years of age. Patients in the SPK group had diabetic-related end-stage renal disease (ESRD) who were on dialysis for a mean period of 17.9 ± 7.5 (range: 3 – 35) months, with a frequency of 2.5 ± 0.5 (range: 2 – 3) times per week. None of the patients had any signs of active infection, recent or current history of malignancy, human immunodeficiency virus (HIV) infection, obesity (body mass index >30), advanced cardiovascular, or peripheral vascular disease. All were negative for HBsAg, HBcAb, and HCV Ab.

The organs (pancreas and kidney in cases of SPK operations) were procured from heart-beating deceased donors in conjunction with multiple-organ retrieval by standard techniques.^{3,4} All donors without hemodynamic and biochemical disturbances were considered eligible. University of Wisconsin solution was used for both *in situ* flush and storage of all organs under cold-storage conditions. Whole organ pancreaticoduodenosplenectomy was performed by an en bloc technique.³ Pancreas cold ischemia time varied from 3.5 to 12 hours. Before transplantation, the pancreas was reconstructed on the back table with a donor iliac artery bifurcation Y graft to the splenic and superior mesenteric arteries.⁵ Duodenal

and arterial preparation, and the remainder of the back table dissection were performed according to the technique previously described by Gaber et al.⁶

Recipients were selected for transplantation based on ABO compatibility, period of time on the waiting list, and a negative T lymphocytotoxic cross-match, in accordance with the United Network for Organ Sharing guidelines (www.unos.org). After preparation of the organ, the recipient operation was performed through a midline intraperitoneal approach. Surgery was based on portal venous drainage and exocrine enteric drainage (P-E drainage). The surgical technique of P-E drainage has been previously described in detail by Gaber et al.⁶ and Shokouh-Amiri et al.⁷ and adopted by personal communications with Professor Shokouh-Amiri. In brief, the portal vein of the pancreas graft is anastomosed end-to-side to a major tributary of the superior mesenteric vein. The donor 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 distally end-to-end to a diverting Roux-en-Y limb of the recipient jejunum.

Then, an attempt is made to anchor the tail of the pancreas to the anterior abdominal wall with interrupted sutures to permit subsequent percutaneous, ultrasound-guided pancreas allograft core biopsies to be performed as needed. In SPK cases by reflecting the peritoneum from the midline incision to the left iliac fossa and exposing the retroperitoneal iliac vessels, a pouch is made to implant the kidney allograft. The renal allograft vessels are anastomosed end-to-side to the left external iliac vessels, followed by an extravesical ureteroneocystostomy by standard techniques. Then, the reflected peritoneum is sutured continuously.

All recipients received primary immunosuppression with tacrolimus (started with 1 mg twice per day at day 1, increased gradually to serum target level of 10-15 ng/dL), mycophenolate mofetil (started with 500 mg twice per day at day 1 and increased to 1000 mg twice per day adjusted to WBC level), and corticosteroids. In the first five cases, we used 1000 mg methylprednisolone IV intraoperatively and at days 1 and 2, tapering to 20 mg prednisolone on day 3, and then decreasing the dose by 2.5 mg per week to 5 mg by the end of the first month. After that, we started prescribing daclizumab (Zenapax®, Nutley, NJ; 1mg/kg/day

for five doses) in the next 10 cases and basiliximab (Simulect[®], Novartis, East Hanover, NJ; 20 mg/dose at day 0 and 4) in the next 25 cases for induction and reduced the induction dose of methylprednisolone to 500 mg/day and after the third dose rapid tapering of oral prednisolone from 20 mg/day to 5 mg/day during the first month after the operation.

The patients were given heparin (300 unit/kg/24 hr as an IV infusion, adjusted to PTT) during the perioperative period till seventh day after the operation to minimize the occurrence of vascular thrombosis and then changed to ASA 325 mg/day started at day 7. Perioperative antibiotic prophylaxis consisted of a preoperative, intraoperative, and three postoperative doses of ceftriaxone (1 g IV every 12 hr). All patients received 480 mg oral trimethoprim/sulfamethoxazole daily for six to 12 months as prophylaxis for *Pneumocystis Carinii*. Antifungal prophylaxis consisted of 200 mg/day of oral fluconazole taken for two to three months. Antiviral prophylaxis included IV ganciclovir (2.5 – 5 mg/kg, twice per day) in the peri-operative period, followed by oral ganciclovir (1 g, three times daily for 100 days after the operation) in the first 20 cases. Thereafter, we switched to pre-emptive treatment of only those patients diagnosed with CMV infection with weekly testing for CMV antigenemia, thereafter.

After transplantation, duplex ultrasonography of the pancreas, the kidney, or both, was performed on the first five postoperative days and as clinically indicated.

Recipients were monitored daily for fasting serum glucose, amylase, lipase, and their renal

profiles, as well as complete blood cell counts. Metabolic control and hormonal profiles were assessed by C-peptide levels, lipid profiles, and glycosylated hemoglobin levels. The diagnosis of rejection was based on clinical criteria, renal allograft dysfunction, serum amylase, glucose and lipase levels, and renal or pancreas allograft histopathology. Pancreas allograft rejection was suggested by an unexplained elevation in serum amylase, lipase, or glucose. Pancreas grafts were considered functioning as long as the recipients were off insulin. A surgical complication was defined as the need for repeat laparotomy within the first three months after the initial operation.

Results

Table 1 shows the demographics and clinical data of the recipients and donors. Among recipients, the male: female ratio was 3:1 (30 men, 10 women) with a mean age of 32.3 ± 8.9 years (range: 16 – 50 years). Thirty-five of the donors were males (male:female ratio= 7:1) with a mean age of 23.6 ± 8.2 years (range: 20 – 28 years). Recipients were followed for a mean period of 10.1 ± 6.5 months (range: 1 – 24 months). Duration of hospital admission was 15.7 ± 7.6 days (range: 8 – 45 days). Length of anesthesia and operation were 7.6 ± 2.1 and 6.4 ± 1.9 hours, respectively. Recipients had 1412.5 ± 947.9 mL estimated blood loss and received 5827.5 ± 1841.0 mL crystalloid fluid during the operation.

During the follow-up period, we had only one mortality due to sepsis three months after the operation because of diffuse concomitant CMV

Table 1. Demographics and preoperative clinical data of the patients according to the type of operation.

	SPK (n=23)	PTA (n=14)	PAK (n=3)
Recipients			
Age	32.1 ± 8.4	30.9 ± 9.2	40.7 ± 9.0
Sex (male/female)	16/7	11/3	3/0
Daily insulin requirement (units)	43.1 ± 14.5	39.6 ± 8.7	67.7 ± 45.9
Creatinine level (mg/dL)	6.41 ± 2.27	$0.94 \pm .16$	1.17 ± 0.25
Duration of hemodialysis (months)	17.9 ± 7.5	*	*
Duration of previous renal graft function (months)	*	*	18.0 ± 5.6
HbA _{1c} (percent)	8.8 ± 1.3	8.7 ± 1.1	8.3 ± 1.3
Donors			
Age	23.5 ± 8.7	23.6 ± 8.3	24.0 ± 6.1
Sex (male/female)	19/4	13/1	3/0
Blood group compatibility(identical/compatible/only Rh different)	20/3/0	9/1/4	0/0/3
Cause of death (trauma/cerebrovascular event/other)	19/3/1	12/2/0	3/0/0

Note: Values expressed as mean \pm SD or number of patients. *not applicable.

and aspergillus infection. This patient was a 49 year old gentleman with a 15-year history of type 1 diabetes. He had been re-explored six hours after the initial operation for diffuse bleeding of unknown cause but the graft had normal function and the patient was insulin independent at the time of patient's death. The graft was resected in three patients during the first week after the operation because of arterial thrombosis, venous thrombosis, and severe rejection, respectively. The graft lost its function in one of the patients after re-exploration for bleeding on the fourth postoperation day, but did not need resection. The remaining recipients ($n=35$, 87.5%) had functioning pancreatic grafts during the follow-up.

Table 2 describes changes in serum biochemical profiles of the recipients with functioning graft before and after PTx up to six months. The mean pretransplant insulin consumption was 43.75 ± 17.40 IU. Patients with a functioning graft became insulin-free, with a mean fasting glucose of 95.6 ± 8.0 mg/dL, HbA_{1c}: $4.6 \pm 0.5\%$ (range: 3.8–5.6), insulin level: 7.0 ± 2.4 μ IU/mL, C-peptide: 5.86 ± 2.13 ng/mL, and a mean serum creatinine level: 1.04 ± 0.26 (range: 0.60 – 1.90) mg/dL at six months postoperation.

All patients with SPK ($n=23$) except for one had immediate kidney graft function, with no need for postoperative dialysis. One patient received a kidney retransplant from a deceased donor two days after the first operation because of venous thrombosis of the renal graft. The pancreas allograft function was not affected.

During the follow-up period, 12 patients had acute rejection episodes (based on fever with pain in the area of the graft with increase creatinine level more than 0.5 mg/dL from baseline in four patients of SPK after ruling out acute vascular events and infection and in others by percutaneous core needle biopsy of the pancreas) which responded to methylprednisolone pulse therapy

except for one of the SPK patients who received Antithymocyte globulin (ATG) because of resistance of kidney rejection to pulse therapy. Rejection was graded according to Drachenberg scale for the pancreas.⁸

Four patients had biopsy-proven chronic rejection after six months which required transient insulin therapy in three and oral hypoglycemic agents in one. Three of these four cases were blood group compatible (not identical) with their donors. Three (all of them PTA cases) had noncompliance with their immunosuppressives after six months. We observed gastrointestinal (GI) complications in 10 patients including six occult GI bleeding, one frank GI bleeding from donor C-loop ulcer, one donor C-loop perforation, one intestinal gangrene due to adhesion band, and chronic diarrhea in another.

Other complications included urinary leakage in one SPK patient, peripancreatic fluid collection with delayed graft function which responded to percutaneous drainage in one patient, and wound infection in another. Figure 1 shows the overall complications of the operation in our patients and Table 3 shows the final endpoints of PTx for each type of operation separately. Graft survival according to Kaplan-Meier model was 84.9% at two years (Figure 2).

Discussion

The American Diabetes Association and the American Society of Transplantation recommend PTx as the treatment of choice for type 1 diabetic patients who have undergone or plan to undergo kidney transplantation.⁹ Nowadays, in major transplant centers around the world, with highly experienced surgical teams, new surgical techniques, and the advent of various immunosuppressive agents, long-term patient and graft survivals are reported and the rates of acute

Table 2. Biochemical profile of the transplanted cases with functioning graft.

	Before Tx	1 st wk post-op	14 days post-op	1 month post-op	6 months post-op
FBS* (mg/dL)	275.47 ± 72.33	128.55 ± 22.27	102.88 ± 10.14	98.38 ± 13.84	95.60 ± 7.97
Amylase (U/L)	—	100.53 ± 44.25	75.24 ± 32.60	80.56 ± 28.49	78.39 ± 26.82
Lipase (U/L)	—	78.24 ± 28.92	68.97 ± 31.37	71.14 ± 23.61	66.03 ± 27.72
C-peptide (ng/mL)	—	6.15 ± 2.27	6.02 ± 1.40	5.81 ± 1.87	5.86 ± 2.13
Insulin level (μ IU/mL)	—	6.05 ± 2.68	5.76 ± 2.17	6.84 ± 2.53	7.02 ± 2.42
HbA _{1c} (percent)	8.76 ± 1.22	4.72 ± 0.58	4.54 ± 0.45	4.69 ± 0.43	4.56 ± 0.53

*FBS=fasting blood sugar; op=operative; Tx=transplantation.

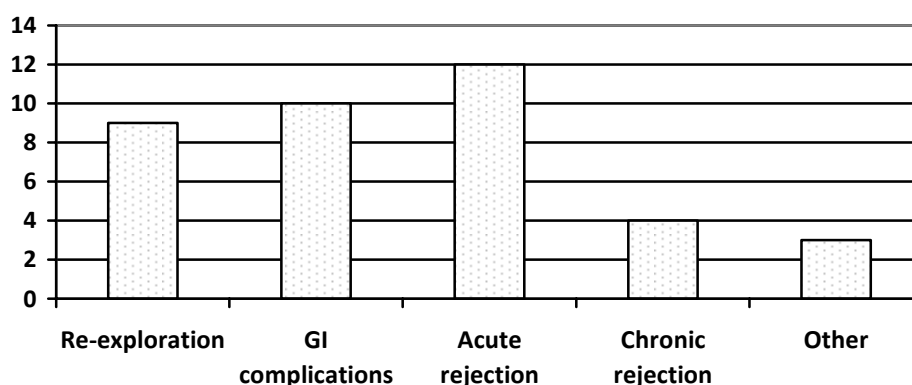


Figure 1. Overall complication rate in PTx patients.

rejection are less than 20% in the first year after transplantation.^{10,11}

The two major standard methods for PTx are systemic venous and bladder drainage method (S-B drainage) and the portal and enteric drainage (P-E drainage) method. In the S-B drainage approach, diversion of pancreatic exocrine secretions into the urinary bladder facilitates monitoring for rejection of the pancreas.¹² Despite its widespread acceptance, the S-B drainage procedure can lead to several surgical and metabolic complications. The surgical drainage of pancreatic exocrine secretion via the urinary bladder provides a constant source of irritation to the bladder mucosa, accentuating the abnormalities associated with autonomic diabetic neuropathy. This environment subsequently leads to chemical cystitis, recurrent hematuria, infection, and repeated episodes of graft pancreatitis.^{13,14} In addition, the elimination of pancreatic exocrine secretions in the urine causes loss of bicarbonate, creates electrolyte derangements, and contributes to dehydration, leading to a state of metabolic acidosis. On the other hand, nowadays whole organ PTx with a

standardized technique of P-E drainage can be performed with results comparable to the conventional technique diversion of pancreatic exocrine secretions into the urinary bladder facilitates monitoring for rejection of the pancreas.¹² Despite its widespread acceptance, the S-B drainage procedure can lead to several surgical and metabolic complications. The surgical drainage of pancreatic exocrine secretion via the urinary bladder provides a constant source of irritation to the bladder mucosa, accentuating the abnormalities associated with autonomic diabetic neuropathy. This environment subsequently leads to chemical cystitis, recurrent hematuria, infection, and repeated episodes of graft pancreatitis.^{13,14} In addition, the elimination of pancreatic exocrine secretions in the urine causes loss of bicarbonate, creates electrolyte derangements, and contributes to dehydration, leading to a state of metabolic acidosis. On the other hand, nowadays whole organ PTx with a standardized technique of P-E drainage can be performed with results comparable to the conventional technique of S-B drainage with patient and graft survival rates, and infectious

Table 3. Outcomes for each type of operation.

	SPK (n=23)	PTA (n=14)	PAK (n=3)	Total (n=40)
Re-exploration	6	3	0	9 (22.5%)
GI complications				
Occult GI bleeding	5	1	0	6 (15%)
Frank GI bleeding	1	0	0	1 (2.5%)
C-loop perforation	1	0	0	1 (2.5%)
Adhesion band	1	0	0	1 (2.5%)
Chronic diarrhea	0	1	0	1 (2.5%)
Graft resection	2	1	0	3 (7.5%)
Acute rejection	7	3	2	12 (30%)
Chronic rejection	1	2	1	4 (10%)
Noncompliance	0	3	0	3 (7.5%)
Graft malfunction	2	2	0	4 (10%)
Death	0	1	0	1 (2.5%)

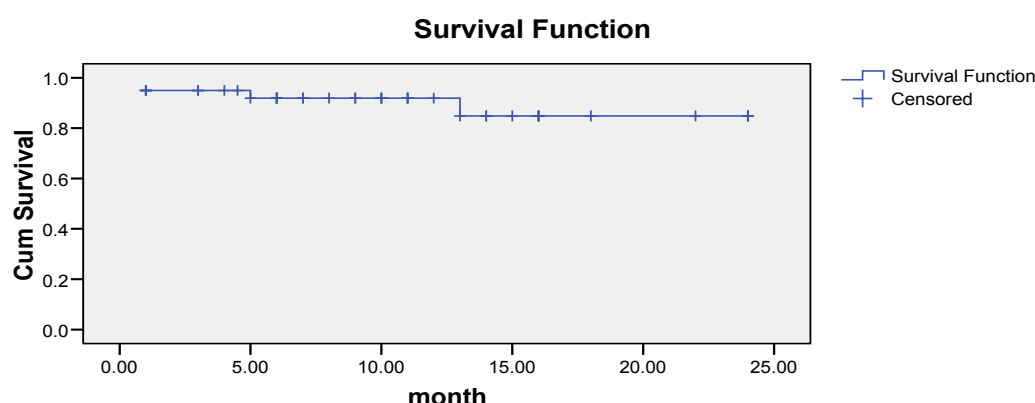


Figure 2. Survival plot of the PTx graft.

complications comparable to S-B drainage technique. In addition, P-E drainage is more physiologic and urinary tract infections and urologic, and metabolic complications are reported to be lower.¹⁵ Because of these, we chose this technique for initiating pancreas transplant program in Shiraz Transplant Center, the main abdominal organ transplant center in Iran with over 15 years of experience in kidney and liver transplantation.

PTx has been associated with the highest surgical complication rate of all the routinely performed organ transplant procedures. Surgical complications are defined as the need for repeat laparotomy within the first three months after PTx. The overall incidence of surgical complications in PTx is reported to be between 10% and 38%.^{16–18} The complications include pancreas graft thrombosis, rejection and ischemic damage, intra-abdominal infection, graft pancreatitis, intra-abdominal bleeding or hematoma, duodenal allograft leakage, and hyperacute/accelerated rejection.¹⁸ In our series, we had nine cases of early re-exploration in the first three months and three cases of surgery for GI complications (C-loop perforation, frank bleeding from C-loop ulcer, and intestinal gangrene from adhesion band) after three months which is comparable with other published results. Because of this late complications and six cases of occult GI bleeding, we changed our policy for intestinal drainage from Roux-en-Y in the first seventeen cases to the loop method and after that we used a loop of jejunum 45 cm from Treitz ligament to perform a side-to-side anastomosis between the C-loop of the donor with the recipient's small intestine. Increasing our

experience in PTx and use of this technique resulted in reduced number of complications, as we had no surgical complications in the last 15 patients.

The risk of pancreas graft loss from surgical complications (technical failures) is higher than from immunologic reasons.¹⁶ In our series, we had four early in-hospital graft loss, three (75%) of them from technical complications, and one from immunologic cause. In the Reddy et al's study¹⁹, the most common surgical complications were intra-abdominal infection (or graft pancreatitis) (38%), pancreas graft thrombosis (27%), and anastomotic leak (15%). We had no anastomotic leakage and no intra-abdominal infection in our series.

PTx provides the most successful clinically available approach to restoring normal homeostasis in patients with type 1 diabetes mellitus who have renal dysfunction or other complications of diabetes. This is the first time that the PTx is performed in Iran. Although this seems to be preliminary experience and we are still on the learning curve, we think we have achieved an acceptable short-term graft and patient survival rates. The goal of our center is to perform more PTx in the following years and make this modality an accessible treatment option for all diabetic patients suffering from ESRD.

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