REVIEW ARTICLE

Pancreas Transplantation

Yi-Ming Shyr*

Divisions of General and Transplantation Surgery, Department of Surgery, Taipei Veterans General Hospital and National Yang-Ming University, Taipei, Taiwan, R.O.C.

The first successful pancreas transplantation in conjunction with a simultaneous kidney transplantation was performed in 1966 by Kelly, Lillehei and others from the University of Minnesota. In Taipei Veterans General Hospital, the first pancreas transplantation (simultaneously coupled with kidney transplantation) was successfully performed on September 19, 2003, and we were qualified to harvest and transplant pancreas graft by the Taiwan Department of Health on August 31, 2007. Currently, pancreas transplantation remains the most effective method of establishing physiological and durable normoglycemia for patients with diabetes mellitus. The main indication for pancreas transplantation is type 1 diabetes with diabetic complications such as nephropathy, retinopathy, neuropathy and cardiocerebral vasculopathy, or with frequent life-threatening hypoglycemia or hyperglycemia. Pancreas graft survival rate at 1 year was 85% for simultaneous pancreas-kidney transplantation, 78% for pancreas-after-kidney transplantation, and 76% for pancreas transplantation alone. At 3 years, pancreas graft survival rates were at least 62% in all categories. [*J Chin Med Assoc* 2009;72(1):4–9]

Key Words: diabetes mellitus, pancreas transplantation, type 1

History of Pancreas Transplantation

The first successful pancreas transplantation in conjunction with a simultaneous kidney transplantation was performed by Richard Lillehei et al, from the University of Minnesota, in 1966, 3 years after the first kidney transplantation.[1] A pancreas along with duodenum was transplanted into a 28-year-old woman and her blood sugar levels decreased immediately after transplantation, but she died of pulmonary embolism 3 months later. In 1979, the first living-related partial pancreas transplantation was done. Until about 1990, the procedure was considered experimental. After animal study done in Taipei Veterans General Hospital,[2] the first pancreas transplantation (simultaneously coupled with kidney transplantation) was successfully performed on September 19, 2003, and we were qualified to harvest and transplant pancreas graft by the Taiwan Department of Health on August 31, 2007. At present, about 1,600–1,800 pancreas transplantations are performed annually in the United States, according to the United Network for Organ Sharing (UNOS) and the International Pancreas Transplantation Registry (IPTR). To date, more than 25,000 pancreas transplants have been performed, mainly in the United States.[3–6] Currently, pancreas transplantation remains the most effective method of establishing physiological and durable normoglycemia for patients with diabetes mellitus (DM).

Classification of Pancreas Transplantation

Traditionally, pancreas transplantations were categorized into 3 types. Table 1 shows a comparison of the 3 types of pancreas transplantations.[7–12]

1. Simultaneous pancreas-kidney transplantation (SPK) is when the pancreas and kidney are transplanted simultaneously from the same deceased donor. About 75–80% of pancreas transplantations are SPK.
2. Pancreas-after-kidney transplantation (PAK) is when a cadaveric or deceased donor pancreas transplantation is performed after a previous, and different, living or deceased donor kidney transplantation. About 10–15% of pancreas transplantations are PAK.

*Correspondence to: Dr Yi-Ming Shyr, Divisions of General and Transplantation Surgery, Department of Surgery, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan, R.O.C.
E-mail: ymshyr@vghtpe.gov.tw • Received: August 26, 2008 • Accepted: November 20, 2008

Table 1. Classification and comparison of pancreas transplantation

Transplant type	Advantages	Disadvantages
Simultaneous pancreas-kidney (SPK), 80%	One operation Similar protocol in immunosuppressants Easier to detect pancreas rejection early by monitoring kidney graft Better outcome	More advanced diabetic complications
Pancreas-after-kidney (PAK), 15%	Already immunosuppressed	Two operations More advanced diabetic complications More difficult to detect pancreas rejection early Mediocre outcome
Pancreas transplantation alone (PTA), 5%	Lower surgical risks with less or no diabetic complications	Early exposure to immunosuppressants More difficult to detect pancreas rejection early Mediocre outcome

3. Pancreas transplantation alone (PTA) is for patients with type 1 DM but adequate kidney function. The remaining 5–10% of cases are PTA.

Indications and Contraindications for Pancreas Transplantation

In patients with type 1 DM, the pancreas no longer produces insulin due to autoimmune destruction of pancreatic islets. In Western countries, the incidence of type 1 DM is high, up to 10–15% of the diabetic population. Currently, the prevalence of type 1 DM in the United States is around 1,100,000 individuals, with 35,000 new cases diagnosed each year. In Taiwan, it is estimated that type 1 DM is about 1–3% of the diabetic population; thus, there are about 6,000–8,000 patients with this disease. At the turn of the 20th century, a patient diagnosed with type 1 DM had an average life expectancy of only 2 years. The development of insulin as a therapeutic agent revolutionized the treatment of DM by changing it from a rapidly fatal disease to a chronic illness. Unfortunately, this increased longevity allowed the development of secondary complications, including nephropathy, neuropathy, retinopathy, and macrovascular and microvascular complications, occurring 10–20 years after disease onset. Currently, no practical mechanical insulin-delivery method, coupled with an effective glucose-sensory device, can replace pancreatic insulin secretion well enough to produce good physiologic control of blood sugar to achieve a constant and near-euglycemic state without the risk of hypoglycemia. The purposes of pancreas transplantation are to produce complete insulin independence, improve the quality and quantity of life, and hopefully to ameliorate or reverse diabetes-related complications. Therefore, it makes sense that pancreas transplantation in a patient with type 1 DM may be able to cure their disease. Pancreas transplantation is rarely indicated for type 2 DM because the major problem there is not a failing pancreas, but the body's inability to respond to insulin in the right way.[8–13]

Pancreas transplantation is a life-enhancing, but not a life-saving, procedure. In addition, the impact of early and long-term exposure to immunosuppressants on a young patient should be taken into consideration. The following sections list the current indications and contraindications for pancreas transplantation in Taiwan.

Indications for pancreas transplantation

- Type 1 DM or low serum peptide with diabetic complications such as nephropathy, retinopathy, neuropathy and cardiocerebral vasculopathy.
- Type 1 DM or low serum peptide with frequent life-threatening hypoglycemia or hyperglycemia.
- Type 1 DM or low serum peptide with disability in learning, working and life.
- Type 2 DM requiring insulin control, but < 1.5 U/kg/day, and kidney transplantation.

Contraindications for pancreas transplantation

- Age > 65 years.
- Uncontrollable infection.
- Human immunodeficiency virus infection.
- Untreated tuberculosis.
- Malignancy, except for the following conditions:
  - intraductal papillary mucinous neoplasm of the pancreas, neuroendocrine tumor of the pancreas, incidental renal carcinoma, *in situ* carcinoma

(excluding bladder), Dukes' A colon cancer, basal cell carcinoma;
  - disease-free interval > 5 years for malignant melanoma, breast cancer, gastrointestinal carcinoma, lung cancer;
  - disease-free interval > 2 years for other malignancies.
- Autoimmune disease treated with prednisolone > 10 mg/day or other immunosuppressants.
- Poor compliance, unresolvable psychosocial problems or severe psychiatric disorder.
- Major medical conditions prohibiting a major operation.
- Uncorrectable severe cardiocerebrovascular or peripheral vascular disorder preventing self-care.
- Drug or alcohol abuse.

Surgical Considerations

Currently, pancreas grafts are mainly from deceased donors with brain death. Exclusion criteria for an ideal pancreas donor include:
- age > 55 years or < 5 years;
- history of diabetes (check HbA1c if DM history is not available);
- history of chronic alcohol abuse, malignancy (except skin or central nervous system), chronic infection, recent intravenous drug abuse;
- prolonged episodes of hypotension;
- high-dose vasopressor use;
- acute systemic infection;
- documented pancreatitis.

Determining donor human leukocyte antigen typing, serologies, and pretransplant lymphocytotoxic crossmatch results with patients on the pancreas transplantation waiting list will permit the ideal situation of allocating the cadaveric pancreas prior to organ procurement. The cold ischemia time of the pancreas prior to implantation should be minimized. Pancreas grafts do not tolerate cold ischemia as well as kidney grafts. Ideally, the pancreas should be revascularized within 24 hours from the time of cross-clamping at procurement.[8–16]

Surgical Techniques

The surgical techniques for pancreas transplantation are diverse, and no standard methodology is used by all programs. The native pancreas is not removed. Pancreas Y-graft arterial reconstruction is prepared on the back table, with anastomosis of the donor internal iliac artery to the graft splenic artery, and the donor external iliac artery to the graft superior mesenteric artery. The arterial Y-graft of the pancreas is usually anastomosed to the recipient right common iliac artery. Positioning of the head of the pancreas graft cephalad or caudad is not relevant with respect to successful arterial revascularization. When pancreas transplantation is performed simultaneously with kidney transplantation, the kidney is usually placed on the recipient left iliac vessels. In some centers, ipsilateral placement of the pancreas and kidney grafts is preferred.[16] Both organs may be transplanted through a midline incision and placed intraperitoneally.[8–10,16]

Two choices are available for venous revascularization: systemic and portal. No clinically relevant difference in glycemic control has been documented between the 2. Currently, approximately 15% of pancreas transplantations are performed with portal venous drainage and the remainder with systemic venous drainage. Systemic venous revascularization commonly involves the distal inferior vena cava, right common iliac vein or right external iliac vein. If portal venous drainage is used, dissecting out the superior mesenteric vein at the root of the mesentery is necessary. The pancreas portal vein is anastomosed end-to-side to a main tributary (usually the iliocolic vein) of the superior mesenteric vein. We prefer to place the pancreas graft retroperitoneally behind the mesocolon of the ascending colon because only a short arterial Y-graft is needed for arterial anastomosis. If the pancreas graft is placed intraperitoneally, the arterial Y-graft should be long enough to be placed through a window in the mesentery to reach the right common iliac artery for arterial anastomosis. Portal venous drainage of the pancreas is more physiologic with respect to immediate delivery of insulin to the recipient liver. This results in diminished circulating insulin levels relative to those in systemic venous-drained pancreas grafts.[8–10,16]

Markers for rejection include clinical signs and symptoms of pancreas graft pancreatitis and measurement of serum blood sugar, amylase or lipase levels coupled with biopsy. Unfortunately, there is no ideal marker to monitor rejection of the pancreas graft because none of the clinical features and serum markers are good enough for early detection of pancreas rejection. The pancreas is sometimes drained into the bladder if a PTA or PAK transplantation is performed in order to measure urinary amylase levels as a method of detecting rejection.[8–10,16]

Pancreatic exocrine drainage is managed by means of anastomosis of a duodenal segment to the bladder or anastomosis to the small intestine. Currently, approximately 80% of pancreas transplantations are performed

with enteric drainage; the remaining 20% are performed with bladder drainage. The bladder-drained pancreas transplantation is a very important modification introduced in about 1985. By monitoring urine amylase level, this technique significantly increases the immediate success rate by easy and early detection of pancreas rejection and improves the safety of the procedure by minimizing the occurrence of intra-abdominal abscess from leakage of enteric-drained pancreas grafts. However, bladder drainage may carry a risk of significant long-term genitourinary tract complications such as bladder infection, cystitis, urethritis, urethral injury, balanitis, hematuria, metabolic acidosis, and reflux pancreatitis. Eventually, about 10–24% of bladder-drained pancreas grafts are converted to enteric drainage. With the successful application of the new immunosuppressants and reduction in the incidence of rejection, enteric drainage of the pancreas transplant has enjoyed a successful rebirth. Enteric drainage of pancreas grafts is physiologic with respect to the delivery of pancreatic juice into the intestine. Enteric drainage of pancreas grafts can be constructed with or without a Roux-en-Y.[8,16]

Immunosuppression Therapy

The principles of immunosuppressant therapy after combined or solitary pancreas transplantation are comparable with those after other solid organ transplantation. There is no doubt that recent developments in immunotherapeutics have played a critical role in transforming pancreas transplantation from a high-risk to a routine treatment. In particular, 2 factors led to improvements in safety and efficacy: (1) the recognition of the advantages of multimodal maintenance immunosuppressive regimens; and (2) the incorporation of modern maintenance agents. However, because of the higher rejection rates in pancreas transplantation, a more potent immunosuppressive regimen is mandatory. At the same time, the careful use of diabetogenic drugs such as steroids and the calcineurin inhibitors is of particular importance. Today, quadruple therapy is the standard immunosuppressive regimen after pancreas transplantation, consisting of an induction and maintenance therapy. The necessity of an induction therapy is most often related to a recipient's high risk of rejection episodes. Another reason to use induction therapy is that it will provide a short course of potent immunosuppression that permits immediate and even permanent elimination of 1 or more of the maintenance agents required post-transplant, such as corticosteroids. So far, no definitive agreement has been reached with regard to what constitutes the single best multimodal strategy.[3,17] The following are common immunosuppressants:

- T-cell immunosuppressants
  - tacrolimus (FK506, Prograft)
  - cyclosporine (Sandimmune, CyA or Neoral)
  - daclizumab (Zenapex)
  - basiliximab (Simulect)
  - muromonab-CD3 (OKT_3)
- B-cell immunosuppressants
  - anti-thymocyte globulin (ATGAM)
  - thymoglobulin (RATG)
- nonspecific immunosuppressants
  - corticosteroids (methylprednisolone, prednisolone, hydrocortisone)
  - mycophenolate mofetil (MMF, CellCept)
  - azathioprine (Immuran, AZA)

Complications

Surgical complications are more common after pancreas transplantation than after kidney transplantation. Nonimmunologic complications of pancreas transplantation account for graft losses in 5–10% of cases. These commonly occur within 6 months of transplantation and are as important an etiology of pancreas graft loss in SPK transplantation as acute rejection is.

Vascular thrombosis is a very early complication, typically occurring within 48 hours and usually within 24 hours of transplantation. This is generally due to venous thrombosis of the pancreas portal vein. The etiology is not defined entirely but is believed to be associated with reperfusion pancreatitis and the relatively low-flow state of the pancreas graft. Prudent selection of donor pancreas grafts, short cold ischemia times, and meticulous surgical technique are all necessary to minimize graft thrombosis.

Transplant pancreatitis occurs to some degree in all patients postoperatively. Temporary elevation in serum amylase levels for 48–96 hours after transplantation is common. These episodes are transient and mild, without significant clinical consequence.

The most serious complication of the enteric-drained pancreas transplantation is leak and intra-abdominal abscess. This serious problem usually occurs 1–6 months after transplantation. Patients present with fever, abdominal discomfort, and leukocytosis. A high index of suspicion is required to make a swift and accurate diagnosis. Percutaneous access of intra-abdominal fluid collection for Gram stain and culture is essential. The flora is typically mixed, with bacteria and often fungus, particularly *Candida*. Broad-spectrum antibiosis

is essential. Surgical exploration and repair of the enteric leak is necessary. A decision must be made on whether the infection can be eradicated without removing the pancreas allograft. Peripancreatic infections can result in development of a mycotic aneurysm at the arterial anastomosis that could cause arterial rupture. Transplant pancreatectomy is indicated if mycotic aneurysm is diagnosed. Occurrence of intra-abdominal abscess has been reduced greatly with increased recognition of the criteria for suitable cadaveric pancreas grafts for transplant. Improved perioperative antibiosis, including antifungal agents, has contributed to the decreased incidence of intra-abdominal infection as well. Perhaps the most significant contribution to reducing the incidence of intra-abdominal abscess is the efficacy of immunosuppressive agents in reducing the incidence of acute rejection and thereby minimizing the need for intensive immunotherapy.[8–10,16]

Gastrointestinal bleeding occurs in the enteric-drained pancreas from a combination of perioperative anticoagulation and bleeding from the suture line of the duodenoenteric anastomosis. This is self-limiting and will manifest as diminished hemoglobin level associated with heme-positive or melanotic stool. Conservative management will suffice.[8–10,16]

Effects of Pancreas Transplantation on Diabetic Complications

Patients with a functioning pancreas graft describe their quality of life and rate their health significantly more favorably than those without. Satisfaction encompasses not only physical capacities but also psychosocial and vocational aspects.

A successful pancreas-kidney transplantation prevents glomerular changes of kidney allografts in patients with type 1 DM. This has been observed in transplanted kidneys of patients undergoing SPK transplantation, as well as in kidneys of recipients undergoing PAK transplantation. These studies provide evidence of the efficacy of normalizing blood glucose and glycosylated hemoglobin levels to prevent the progression of diabetic glomerulopathy in renal allografts. Furthermore, successful pancreas transplantation will halt or reverse the pathology in the native kidneys of patients with type 1 DM and very early proteinuria.[8–10,12,16]

Motor-sensory and autonomic neuropathy was reported to be halted and, in many cases, reversed 1–2 years after a successful pancreas transplantation. However, this raises the possibility that improvement of diabetic neuropathy occurs, in part, because of improvement in uremic neuropathy after a pancreas-kidney transplantation. However, PTA in pre-uremic patients has also been shown to result in improvement in diabetic neuropathy. Many patients express subjective improvements in peripheral sensation 6–12 months after pancreas transplantation.[8–10,12,16]

Pancreas transplantation does not show an immediate dramatic beneficial effect on pre-established diabetic retinopathy. Retinopathy appears to progress for at least 2 years following pancreas transplantation, but it begins to stabilize in 3–4 years compared to diabetic recipients of kidney transplantation only.[8–10,12,16]

Outcomes After Pancreas Transplantation

According to IPTR and UNOS, patient survival at 1 year after deceased donor pancreas transplantation was at least 95% in all categories and highest in PTA, with 95% in SPK, 95% in PAK, and 98% in PTA, and at least 88% in all categories at 3 years.[3–6]

Statistically and clinically, the outcome of kidney transplantation is significantly superior in patients who receive SPK transplant versus patients with type 1 DM who receive kidney transplantation alone. Pancreas graft survival rate at 1 year after deceased donor transplantation was 85% for SPK transplantations; kidney graft survival was at least 89%. For solitary pancreas transplantations, pancreas graft survival rate at 1 year was nearly equal: 78% for PAK and 76% for PTA. At 3 years, pancreas graft survival rates were at least 62% in all categories.[3–6]

Rejection rates at 1 year have steadily decreased and are currently in the 10–20% range, depending on case mix and immunosuppressive regimen. The 1-year rates of immunologic graft loss have decreased to 2.6% after SPK, 7% after PAK, and 9.7% after PTA.[3]

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