

Simultaneous pancreas-kidney transplantation with modified enteric drainage of exocrine pancreatic secretion

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BACKGROUND: As a valid therapeutic option for patients with type 1 diabetes mellitus (IDDM) and secondary diabetic nephropathy, simultaneous pancreas-kidney transplantation (SPK) remains more undeveloped than other solid organ transplantations due to the restrictions of surgical techniques especially the modes of exocrine pancreatic secretion. The aim of this paper was to summarize our single-center experience in SPK with modified enteric drainage (ED).

METHODS: From June 2000 to July 2003, 10 patients with IDDM associated with uremia received SPK. The pancreatic allograft exocrine secretion was drained into the proximal jejunum via a side-to-side duodenojejunostomy without Roux-en-Y anastomosis. Quadruple immunosuppressive regimen consisted of induction of tacrolimus (TAC)/cyclosporine (CsA), mycophenolate mofetil (MMF), steroids and antibodies, which included antilymphocyte globulin (ALG) or anti-CD25 monoclonal antibody.

RESULTS: ED-SPK without Roux-en-Y anastomosis was successful in all 10 patients without serious complications such as pancreatitis, graft thrombosis and pancreatic fistula. The patients regained immediate kidney allograft function and euglycemia with insulin-independence. Four patients survived over one year. Episodes of acute rejection were observed in 4 patients, 3 of whom showed reversion after treatment of OKT3 or insulin. Early postoperative complications included peritoneal infection (2 patients), wound infection (2) and renal hematoma (1).

CONCLUSION: ED-SPK without Roux-en-Y anastomosis is safe and preferable to the patients with IDDM associated with uremia.

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Introduction

Simultaneous pancreas-kidney transplantation (SPK) has become a widely accepted therapeutic option for patients with type 1 diabetes mellitus (IDDM) and end-stage diabetic nephropathy. This procedure aims to consistently establish an insulin-independent, normoglycemic state, and thereby prevent the secondary complications of diabetes and improve the life quality of the patients.^[1,2] Patient survival has been shown more markedly in recipients of SPK than in those of kidney transplantation alone.^[3] By the end of 2002, a total of 14 161 cases received combined transplantation of pancreas-kidney allograft all over the world. In China, the first SPK was performed at our institution in 1989^[4] and the total number of recipients has exceeded 100 by the end of 2002.

The ideal surgical technique for drainage of exocrine pancreatic secretion remains uncertain since Kelly and Lillehei performed the first SPK for diabetic nephropathy in 1966. Various procedures have been proposed, such as injection of a synthetic polymer in the pancreatic duct, bladder drainage (BD) of exocrine secretion and enteric drainage (ED) of exocrine secretion. BD-SPK, which was used worldwide in the last decade, has been proven to eventually result in severe metabolic complications and recurrent urinary tract infections in some patients. Many of these patients require conversion from BD to ED, necessitating a second operation. Thus ED-SPK, which is more physiological, is preferred recently. This report describes our experience with uremia diabetic patients who received modified ED-SPK without Roux-en-Y procedure.

Methods

Table. Characteristics of ED-SPK recipients

Patient number	Age (y)	Sex	Date of transplant	Duration of IDDM (y)	Pre-transplant complications	Duration of dialysis (m)	HLA mismatch
1	32	F	00.6.26	10	Retinopathy/blindness	12	1
2	44	M	00.9.8	27	Hypertension	8	3
3	54	M	00.9.22	20	Hypertension	5	2
4	51	F	01.9.24	23	Macroangiopathy	5	1
5	43	F	02.6.8	16	Cardiomyopathy retinopathy/blindness	9	3
6	45	M	03.1.13	13	Retinopathy	3	4
7	47	F	03.4.24	6	Retinopathy	4	4
8	40	M	03.4.30	13	Hypertension	6	2
9	47	M	03.7.11	10	Retinopathy/blindness	18	1
10	36	M	03.7.16	7	Optical neuritis	7	3

Study population

Between June 2000 and July 2003, ED-SPK was performed in 10 recipients (4 women and 6 men) with a mean age of 43.9 years (range: 32-54 years) at our institution (Table). Their mean duration of IDDM was 14.5 years (range: 6-27 years) and their mean duration of end-stage renal failure was 7.7 months (range: 3-18 months). All of these patients were subjected to transplantation based on ABO blood group compatibility and negative cross-matching test.

Organ procurement, preservation and preparation

The pancreas and kidney were procured from cadaveric donors in conjunction with multiple organ retrieval using standardized techniques. University of Wisconsin (UW) solution was used for both in situ flush and storage of all organs under cold storage conditions. The whole organ involving the pancreaticoduodenum, spleen and kidney was procured by an en bloc technique. Cold ischemia was kept to a minimum and preservation time of the pancreas was below 24 hours in all cases. The spleen was left attached to the tail of the pancreas to be used as a handle. The kidney was likewise prepared using standard techniques. The pancreaticoduodenal graft was repackaged separately and in sterile fashion in cold UW solution prior to implantation.

Recipient operation^[5,6]

The kidney graft was transplanted first into the left iliac fossa, followed by an extra-vesical ureteroneocystostomy protected with a double pigtail ureteral stent for 2 weeks. Foley catheter bladder drainage was maintained for 1 week. The whole pancreas and duodenum segment grafts were put into the peritoneal cavity. The donor superior mesenteric and splenic arteries constituting Carrel patch were anastomosed end-to-side to the recipient right external iliac artery, and the portal vein was anastomosed to the external iliac vein. The duodenal segment of the pancreas allograft was then sutured in a side-to-

side fashion to the recipient mid-jejunum instead of to a diverting Roux-en-Y limb by using a two-layer hand-sewn technique of inner running 3-0 absorbable suture and outer 3-0 silk interrupted suture. The total operative time lasted about 6 hours.

Immunosuppressive protocols

In all SPK patients, immunosuppression was achieved by quadruple prophylactic association. Two patients were treated with anti-lymphocyte globulin (ALG) which was given intravenously within 12-24 hours after transplant and then daily for a total of 8-10 doses for induction therapy. The other 8 patients who were transplanted in the latest period received IL-2 receptor antibodies (Zenapax, Roche, USA) instead of ALG, in a dose of 50 mg i. v. on day 0 and day 14 after transplant. Maintenance immunosuppression consisted of calcineurin inhibitors (cyclosporine or tacrolimus), mycophenolate mofetil (MMF), and steroid, which were given within 48 hours postoperatively. Tacrolimus (TAC) was administered at a dosage of 0.1 mg · kg⁻¹ · day⁻¹ orally in two divided doses. TAC was titrated to a 12-hour trough level of 8-12 ng/ml for the first 3 months after transplant, then the blood levels of TAC were maintained at 5-10 ng/ml. Oral MMF was given at a dosage of 1.5-2 g/d in two or three divided doses. The MMF dose was reduced in patients with gastrointestinal intolerance (nausea, vomiting, or diarrhea) or in those when their total white blood cell count was less than 3000/mm³. MMF administration was discontinued temporarily in patients with active infection or septicemia, or when their total white blood cell count was less than 2000/mm³. It was resumed later at a reduced dosage. Corticosteroids included intravenous methylprednisolone (500 mg) during surgery with rapid decrease to oral administration of 15 mg on day 14 and 5-10 mg 6 weeks after transplant.

Diagnosis and treatment of rejection

The diagnosis of rejection was based on clinical criteria, renal allograft dysfunction, serum amylase and lipase levels, serum glucose levels, and allograft histopathology. Renal allograft rejection was suggested by an unexplained rise in serum creatinine of 25% from baseline level and confirmed by ultrasound-guided percutaneous biopsy. Pancreas allograft rejection was suggested by an unexplained elevation in serum amylase or lipase of $\geq 50\%$ or unexplained hyperglycemia and confirmed by ultrasound-guided percutaneous biopsy. The severity of rejection was defined according to the Banff criteria^[7] for kidney biopsies and by a modification of the Maryland classification^[8] of allograft rejection for pancreas biopsies. All biopsy-proven rejection episodes were treated according to their severity. Mild allograft rejection episodes were treated with intravenous methylprednisolone (500 mg/d for 3-5 doses) and rejections resistant to steroids were treated with a 7-14-day OKT3 course.

Perioperative monitoring and medication

Patients were monitored in the ICU for 3-5 days before being transferred to the Transplant Unit. After transplantation, the recipients were monitored for daily fasting serum glucose, amylase and lipase levels, coagulant profiles, renal function, CsA or TAC level and complete blood cell count. Metabolic control and hormonal profiles were assessed by intravenous glucose tolerance testing, fasting and stimulating C-peptide levels and lipid profiles. Duplex ultrasonography or NMR imaging of the kidney pancreatic allograft was performed on the first postoperative week and whenever clinically indicated.

For perioperative prophylaxis, cefotaxime was used for 5 days. Heparin and dextran 40 were given intravenously as continuous anti-coagulants to prevent thrombosis and improve microcirculation in the glomerulus. Stilamin and sandostalin were involved in the procedure to prevent graft pancreatitis.

Results

In 9 patients the pancreatic allograft functioned immediately, and these patients maintained normal blood glucose measurements after the transplant. The incidence for delayed graft function, which is defined as the need for exogenous insulin at the time of discharge after pancreas transplant, was seen in one patient. Oral glucose tolerance test performed two weeks later showed that the patients gained euglycemia with insulin-independence. The post-transplant results of oral glucose tolerance test and serum insulin secretion test are shown in Fig. The kidney grafts in all 10 patients had immediate function and the baseline Scr was kept at a mean level of $104.6 \pm 18.3 \mu\text{mol/L}$ (range: 64.2-139.6 $\mu\text{mol/L}$) in

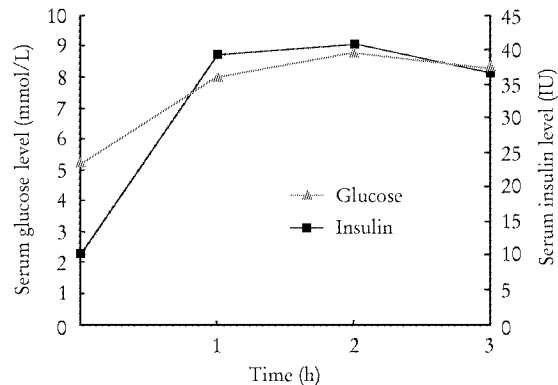


Fig. Results of OGTT and insulin secretion test after ED-SPK.

10 days after operation. The patients have been followed up for 2 to 39 months. Episodes of biopsy-confirmed acute rejection were seen in 4 patients between 20 days and 12 months after transplant, 3 of whom showed successful reversion after rescue therapy with high-dose steroid or OKT3. Nevertheless, graft loss appeared in the other patient with steroid-resistant rejection and the second kidney transplantation was performed subsequently. One female patient died from cardiac arrest at 6 months post-transplant with functional pancreas and kidney grafts.

Peritoneal infection, which is defined as the combination of intra-abdominal germ identification with leucocytosis and fever, as well as wound infection was seen in 2 patients, respectively. All of them required initial or change of antibiotherapy and/or surgical or percutaneous drainage. One patient complicated by renal hematoma was subjected to surgery. All of the 10 patients were free from serious complications such as pancreatitis, graft thrombosis and pancreatic fistula.

Discussion

Surgical consideration

As the most valid therapeutic procedure for IDDM patients with end-stage nephropathy at present, SPK may not be perfect because of the complexity of surgical methods in dealing with unnecessary exocrine pancreatic secretion. Clinical pancreas transplantation has been directly influenced by the development and application of various surgical techniques since the first SPK in 1966.^[9]

From 1987 through 1995, most SPKs were performed with BD by the duodenal segment technique. The advances in preservation, donor selection and immunosuppression, which place the duodenal segment at a lower risk for ischemic or immunological injury, have rekindled the interest of surgeons in primary ED. Since 1995, the number of ED-SPK has steadily increased, with results comparable to those of BD-SPK.^[10-15] ED-SPK is marked by a 20% incidence of urinary tract-relat-

ed complications associated with BD-SPK.^[10] BD has resulted in severe acidosis secondary to bicarbonate wasting, dehydration, hematuria, and recurrent urinary tract infection. Many of these patients require conversion from BD to ED and need a second operation.^[16,17] Thus ED is preferred for SPK recipients.

The first case of ED-SPK in China was reported in 2000.^[18] Since then, this kind of surgical procedure has been adopted in a few transplant centers.^[19] Nevertheless, the general results were not satisfactory because of serious surgical complication as a major obstacle for a successful operation.^[20] Since 2000, we have modified the mode of ED by suturing the duodenal segment of the pancreas allograft to the recipient mid-jejunum rather than to a diverting Roux-en-Y limb in the ten SPK recipients, thus making the operation simpler. All of these patients have got euglycemia and been completely free from exogenous insulin after transplantation. Contrary to the general perception, the ED technique is not technically demanding, nor is it associated with a higher incidence of surgical complications. In this study, no pancreatitis and pancreatic fistula were observed except peritonitis appeared more frequently in 2 patients after SPK.^[21] It is shown that modified ED-SPK is compatible with BD-SPK accompanied with improved surgical procedures in terms of efficacy and safety profiles. Apart from reducing graft injury to the pancreas during the procurement, preservation and preparation, better circulation in the duodenal segment and effective inhibition of pancreatic allograft exocrine secretion are of vital importance to a successful operation. SPK from living-related donor offers a better immunologic match and reduces ischemic injury.^[22] Because of the shortage of allograft, SPK is also performed with grafts from controlled non-heart-beating donors, thus increasing the number of transplants.^[23]

Immunosuppressive protocol selection

In addition to the refinement of surgical techniques in the past few years, the development of immunosuppressive protocol, for example, the wide use of TAC and MMF, is another factor for decreasing the incidence of allograft rejection and improving the result of SPK.^[24,25] The safety and efficacy of combined TAC and MMF in kidney and liver transplantation have extended their use in SPK patients. Clinical trials on the simultaneous use of TAC and MMF in combination with antibody induction showed favorable results in pancreatic transplantation recipients, with an incidence of 10% to 40% for acute rejection after SPK.^[26-29] In this study, combined TAC and MMF was introduced in 9 recipients except one who was intolerable to TAC and the incidence of rejection was similar to that reported above. Accumulated experience with combined use of TAC and MMF and lowered rate of acute rejection have justified the combination of TAC and MMF in post-SPK immu-

nosuppression.^[30] Antibody induction therapy which is usually involved in immunosuppression post-SPK to suppress rejection without renal injury is controversial. The data from the UNOS registry have shown that the survival rates of kidney and pancreas grafts and patients after SPK are not significantly different in recipients with or without either polyclonal or monoclonal anti-T-lymphocyte induction therapy.^[10] In spite of favorable outcomes in SPK patients receiving TAC and MMF without antibody induction, most centers are reluctant to eliminate induction therapy because of the increased possibility of acute rejection that will affect the long-term graft survival. Sirolimus, a new potent immunosuppressive agent, appears to be safe and effective in SPK transplantation with excellent survival rates of patients and grafts, which compare favorably to those of current treatments.^[31,32]

A recent follow-up for 3 to 46 months has shown that 9 of the 10 patients are both dialysis- and insulin-free, suggesting that ED-SPK and TAC/MMF immunosuppression may result in excellent intermediate outcomes and may soon become a standard practice because of its potential physiological and immunologic advantages.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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