

Total Pancreatectomy and Autologous Islet Cell Transplantation as a Means to Treat Severe Chronic Pancreatitis

Horacio L. Rodriguez Rilo, M.D., Syed A. Ahmad, M.D., David D'Alessio, M.D., Yasubiro Iwanaga, M.D., Joseph Kim, M.D., Kyuran A. Choe, M.D., Jonathan S. Moulton, M.D., Jill Martin, Pharm.D., Linda J. Pennington, R.N., Debbie A. Soldano, R.N., Jamie Biliter, Pharm.D., Steve P. Martin, M.D., Charles D. Ulrich, M.D., Lebel Somogyi, M.D., Jeffrey Welge, Ph.D., Jeffrey B. Matthews, M.D., Andrew M. Lowy, M.D.

Autologous islet cell transplantation after near-total or total pancreatic resection can alleviate pain in patients with severe chronic pancreatitis and preserve endocrine function. From February 2000 to February 2003, a total of 22 patients, whose median age was 38 years, underwent pancreatectomy and autologous islet cell transplantation. Postoperative complications, metabolic studies, insulin usage, pain scores, and quality of life were recorded for all of these patients. The average number of islet cells harvested was 245,457 (range 20,850 to 607,466). Operative data revealed a mean estimated blood loss of 635 ml, an average operative time of 9 hours, and a mean length of hospital stay of 15 days. Sixty-eight percent of the patients had either a minor or major complication. Major complications included acute respiratory distress syndrome (n = 2), intra-abdominal abscess (n = 1), and pulmonary embolism (n = 1). There were no deaths in our series. All patients demonstrated C-peptide and insulin production indicating graft function. Forty-one percent are insulin independent, and 27% required minimal amount of insulin or a sliding scale. All patients had preoperative pain and had been taking opioid analgesics; 82% no longer required analgesics postoperatively. Pancreatectomy with autologous islet cell transplantation can alleviate pain for patients with chronic pancreatitis and preserve endocrine function. (*J GASTROINTEST SURG* 2003;7:978-989) © 2003 The Society for Surgery of the Alimentary Tract

KEY WORDS: Pancreatectomy, autologous islet transplantation, quality of life, chronic pancreatitis

Chronic pancreatitis is a disease that progressively destroys pancreatic exocrine tissue, causes pain syndromes that frequently require hospitalization, and can severely compromise quality of life. Medical management consisting of analgesics and pancreatic enzyme replacement rarely leads to acceptable relief of pain and can often act as a precursor to the abuse of narcotics.¹ Patients who suffer from chronic pancreatitis are at increased risk for pancreatic adenocarcinoma relative to the general population.^{2,3}

At least 50% of patients who suffer from chronic pancreatitis will ultimately require some form of surgical intervention⁴⁻⁶ secondary to persistent refractory

pain and/or complications of the disease.^{7,8} The selection of specific surgical procedures to treat chronic pancreatitis are generally based on the presenting characteristics of each patient, including baseline endocrine and exocrine function, pancreatic and ductal pathology, and intensity of pain.⁹ Among patients undergoing surgery, 30% to 50% will develop recurrent symptoms or complications related to pancreatic disease, despite initially successful surgical intervention. Additional operative intervention for resection or drainage may then be indicated.¹⁰⁻¹⁸ Another subset of patients who initially present with small duct disease are not thought to be suitable candidates

Presented at the Presidential Plenary Session, at the Forty-Fourth Annual Meeting of The Society for Surgery of the Alimentary Tract, Orlando, Florida, May 18-21, 2003 (oral presentation).

From The Pancreatic Disease Center, the Departments of Surgery (H.L.R.R., S.A.A., Y.I., L.J.P., D.A.S., J.B.M., A.M.L.), Gastroenterology (S.P.M., C.D.U., L.S.), Radiology (K.A.C., J.S.M.), Endocrinology (D.D.), Psychiatry (J.W.), and Pharmacy (J.M.), University of Cincinnati College of Medicine, Cincinnati, Ohio.

Reprint requests: Horacio L. Rodriguez Rilo, M.D., Associate Professor of Surgery and Pediatrics, University of Cincinnati, 231 Bethesda Ave., P.O. Box 670558, Cincinnati OH 45267-0558. e-mail: Rilohl@uc.edu

for partial pancreatectomy or duct decompression procedures.

In these patients for whom both medical and standard surgical management is deemed inappropriate or has failed to provide relief, total pancreatectomy may alleviate symptoms of debilitating pain.¹⁹ Although morbidity and mortality rates associated with this procedure have decreased markedly during the past 25 years,²⁰ most clinicians do not consider total pancreatectomy to be a therapeutic option because patients often develop "brittle" diabetes, which is extremely difficult to manage. Autologous islet cell transplantation after near-total or total pancreas resection, however, may offer a means to preserve endocrine function while alleviating the debilitating pain associated with severe chronic pancreatitis.^{21,22} It is estimated that roughly 30% to 50% of patients who forgo surgery for chronic pancreatitis will become diabetic nonetheless.^{5,23,24}

Autologous islet cell autotransplantation was first described 30 years ago as a means of preventing diabetes after total pancreatectomy,²⁵ with various sites of implantation attempted in animal and human models.²⁵⁻³⁴ The feasibility of autologous islet cell transplantation after pancreatectomy was first demonstrated in 1977 in a 39-year-old female patient who suffered from familial pancreatitis. After the procedure, she remained insulin independent and pain free for the remainder of her life (6 years).³⁵ Since that time the body of literature on the subject has remained comparatively limited with only 15 centers worldwide reporting on their experiences to the International Islet Transplant Registry.³⁶ According to 2001 data, 140 islet cell autotransplants after pancreatectomy were performed between 1990 and December 31, 2000. Of these, 93 cases were performed at four institutions. The current approach involves infusion of islet cells isolated into the portal vein following pancreatectomy and distribution throughout the liver. In the best-case scenario, patients no longer need insulin and have normal glucose tolerance,^{25,37} although some patients with less optimal outcomes require exogenous insulin to treat hyperglycemia.^{31,32,35,38}

In this report we describe 22 consecutive cases of near-total to total pancreatectomy with simultaneous islet cell autotransplantation for patients suffering from chronic pancreatitis in which other treatment options were no longer considered feasible.

MATERIAL AND METHODS

Patients

From February 2000 to February 2003, a total of 22 patients (15 females and 7 males) were referred

to the Pancreatic Disease Center (PDC) at the University of Cincinnati for treatment of chronic pancreatitis and subsequently underwent total, completion, or near-total pancreatectomy with immediate islet cell autotransplantation.

The diagnosis of chronic pancreatitis was based on the patient's history, results of laboratory tests, computed tomography (CT) scans, endoscopic retrograde cholangiopancreatography (ERCP), and in some patients, pathologic confirmation. Intractable pain was a symptom that was shared by all patients, and all of them used narcotics on a chronic basis for analgesia. All operations were performed under the guidance of one of three attending surgeons. All patients signed informed consent forms that had been approved by the institutional review board of the University of Cincinnati for the surgical procedure, autologous islet cell transplantation, and in most cases pre- and postoperative metabolic testing. All of the patients underwent CT scanning and chest roentgenography. For patients requiring splenectomy, vaccinations for *H. influenza* and *Pneumococcus* was given.

The PDC database was reviewed for standard demographic data. The hospital course of each patient was reviewed to identify the indications for surgery, pathologic findings, perioperative complications, and length of hospital stay. Operative data recorded included estimated blood loss, which was determined jointly by the attending surgeon and staff anesthesiologist, and the length of the surgical procedures.

Operative Procedures

The technique used for near-total pancreatectomy involved removing the entire pancreas except for a small rim (<5%) along the duodenal C-loop that was left intact along with the common bile duct and pancreaticoduodenal arteries. The technique of total pancreatectomy involved removing the entire pancreas along with the spleen, duodenum, and distal common bile duct. Preservation of the pylorus was at the discretion of the attending surgeon. Gastrointestinal reconstruction involved either a side-to-side two-layer gastrojejunostomy or an end-to-side duodenojejunostomy. Bile duct continuity was usually restored by an end-to-side hepaticojejunostomy just proximal to the gastrojejunostomy.

During the operative procedure, the blood supply to the pancreas was preserved for as long as possible during the mobilization and resection process to minimize warm ischemia to the islet cells. Typically the distal portion of the pancreas was mobilized initially and divided, along with the splenic artery and vein, at the level of the superior mesenteric vein; this portion was then preserved and processed for islet cell harvest,

while the remainder of the pancreas was mobilized and resected.

An intravenous insulin drip was started immediately after the pancreatic resection to maintain blood glucose levels less than 120 mg/dl. This was done to prevent acute metabolic decompensation and to provide a more favorable environment for the return of the islet cells, inasmuch as the detrimental effects of hyperglycemia on islet cell engraftment have been demonstrated in animal studies.^{39,40} Finally, gastrostomy and jejunostomy tubes were placed at the discretion of the attending surgeon.

Islet Cell Preparation

A separate back table was prepared in the operating room to handle the resected pancreas. The excised gland was placed in a bowl containing University of Wisconsin (UW) solution iced to 4° C to better preserve it and to minimize cold ischemic damage to the pancreas. While still submerged in cold UW solution, the pancreas was detached from the duodenum (if present), spleen, and any excess retroperitoneal fat. If patent, the pancreatic duct was then cannulated with an appropriate-gauge angiocatheter. The dissected gland was transported to the laboratory for further processing and distended with a solution containing Liberase (Roche Molecular Biochemicals, Indianapolis, IN).

Islet cells were liberated from the remaining exocrine tissue through the use of continuous cold enzymatic perfusion and digestion as previously described.⁴¹ Briefly, pancreatic tissue was mechanically and enzymatically dissociated in a digestion chamber in the presence of a recirculating solution containing collagenase. The solution was recirculated using a roller pump, and the temperature of the fluid was maintained as close to 38° C as possible to sustain optimum digestion. When digestion was completed (islet cells were adequately liberated from the remaining exocrine tissue), the flow was rerouted to a separate collecting flask where the majority of enzymatic reactions were arrested by both diluting the islet-containing solution and lowering its temperature to 7° to 10° C.

Islet Cell Transplantation

While the islet cells were being harvested, the operating surgeons completed the pancreatic reconstruction. Approximately 3 hours after pancreatectomy, the recovered islet cells were transplanted into the liver. Islet cell infusion was performed in one of two ways: either through a middle colic venous tributary or directly into the portal vein. All of the

patients received 5000 IU intravenous heparin immediately preceding infusion of pancreatic islet cells. Portal venous pressure was selectively measured, depending on the volume of digested pancreatic tissue and islet cells. Arterial and central venous pressures were monitored in all patients.

Metabolic Studies

Preoperatively, patients were referred to the Clinical Research Center at the Cincinnati Children's Medical Center for metabolic testing. After an overnight fast, intravenous catheters were placed into veins in both forearms. Following removal of fasting blood samples, subjects received 5 g of arginine as a bolus infusion over 60 seconds, and serial blood samples were obtained over a 15-minute period. After a 30-minute rest period to allow islet hormones to return to steady-state baseline, blood samples were again drawn, 75 g of glucose solution was then ingested over 5 minutes and blood samples were taken over 3.5 hours. Plasma was removed and stored at -30° C. Metabolic testing was repeated 3 to 4 months postoperatively. Plasma glucose level was measured using a glucose oxidase method, and insulin and C-peptide concentrations were determined using radioimmunoassay. Pre- and postoperative values for each subject were determined in the same assay.

The acute insulin/C-peptide response to arginine was computed as the area under the hormone response curve above fasting. The glycemia and insulin responses to the oral glucose load were calculated as the area under the glucose and insulin response curves over the period of sampling.

Post-Transplant Care

Postoperative care was undertaken in the surgical intensive care unit for the first 24 hours, with hourly glucose monitoring to ensure blood glucose levels between 100 and 120. Patients were given intermittent injections of insulin as required for glycemic control. Postoperative pain was controlled with either an epidural analgesic catheter or a patient-controlled analgesic pump. An oral diet was reinstated when gastrointestinal motility returned.

Pain Assessment and Quality of Life

Follow-up data regarding narcotic usage, insulin regimens, pain assessment, and quality of life were collected during postoperative clinic appointments; information was obtained via a written questionnaire and by direct follow-up phone contact. The SF-36 Health Survey (SF-36)⁴² was administered to assess quality of life. The McGill Pain Questionnaire

(MPQ)⁴³ was administered to evaluate pain. Because patients used a variety of analgesics for management of pain, for the sake of analysis and comparison morphine equivalent doses were obtained using the Pharmacokinetics of Narcotic Agonist Analgesics table as listed in *Drug Facts and Comparisons 2003* and the Narcotic Agonists Comparative Pharmacokinetics table listed in the *Drug Information Handbook 2002–2003*. *t*-tests were used to analyze pre- and postoperative information. These studies were approved by the institutional review board of the University of Cincinnati Medical Center, and written consent was obtained from all patients included in the study. The questionnaire included five general questions about the location and intensity of the pain, other analgesics or pancreatic enzymes being taken, and employment. In addition, patients were asked to answer 10 questions comparing pre- and postoperative levels in health, mood, activities, and pain (SF-36). Each response was graded as follows: -10 = increased/worsened pain level; 0 = no change; and $+10$ decreased/improved pain level.

The primary end points for the study included improvement in patients' quality of life and pain after pancreatectomy and autoislet infusion. A secondary outcome included decrease in the amount of analgesics and pancreatic enzymes used by the patients after surgery. Employment before and after surgery was also included as an outcome measurement.

Statistical Analysis

Distribution of quantitative measures was inspected graphically to verify parametric assumptions (e.g., normality) and results are summarized as the arithmetic mean, standard deviation, and range unless otherwise noted. Patients were classified dichotomously according to whether postoperative insulin independence was achieved. Potential associations of categorical patient attributes (e.g., sex) with this binary outcome were evaluated by means of Fisher's exact test. Differences with respect to quantitative measurements between patients who achieved insulin independence and those who did not were tested with *t*-tests. Associations between quantitative measures were graphically inspected for possible nonlinearities using scatter plot displays. Unless otherwise noted, the magnitudes of linear associations are summarized by the square of the Pearson correlation coefficient (*R*), which is interpreted as the proportion of the variation in one variable that can be predicted from the other variable (i.e., $R^2 = 1.0$ implies perfect prediction).

RESULTS

Patients

From February 2000 to February 2003, a total of 22 patients underwent partial or total pancreatic resection with immediate autoislet transplantation. Fifteen of these patients were females with a median age of 40 years (range 16 to 62 years), and seven were males with a median age of 36 years (range 22 to 53 years). Eighteen patients (82%) had idiopathic pancreatitis. Of these 18 patients, 32% ($n = 7$) were found to have pancreas divisum, but this could not be definitively linked as a cause of pancreatitis. Idiopathic pancreatitis was a diagnosis of exclusion after all other causes were rejected. Other causes of pancreatitis in our series included alcohol-induced pancreatitis in two patients, post-ERCP pancreatitis in one patient, and trauma-induced pancreatitis in one patient. Indications for surgery included pain that was refractory to high-dose opioid analgesics (all 22 patients) and recurrent acute pancreatitis (3 of 22 patients), with documented amylase and/or lipase elevations.

During this period 12 patients underwent total pancreatectomy as their initial procedure, seven patients underwent completion pancreatectomy, and three patients underwent partial pancreatectomy. Partial pancreatectomy procedures included subtotal pancreatectomy ($n = 1$) and pancreaticoduodenectomy ($n = 2$). Of the patients undergoing completion pancreatectomy, four had undergone a previous subtotal pancreatectomy and three had undergone a previous Whipple procedure. In addition, of the patients undergoing completion pancreatectomy, two had also undergone a lateral pancreaticojejunostomy. Of the 12 patients undergoing total pancreatectomy as their initial procedure, two had undergone a lateral pancreaticojejunostomy (Table 1). All patients with an intact sphincter of Oddi at the time of their islet cell transplantation ($n = 17$) had undergone an ERCP, and of these patients seven also had prior sphincterotomy and stent placement.

Perioperative Results

Analysis of operative data demonstrated a mean estimated blood loss of 635 ml (range 50 to 2200 ml). The average operative time was 9 hours (range 5 to 12 hours). The average length of hospital stay for these patients was 15.2 days, with a range of 5 to 40 days.

Sixty-eight percent of patients had postoperative complications. Major complications included pulmonary embolism ($n = 1$), acute respiratory distress syndrome ($n = 2$), and intra-abdominal abscess ($n = 1$). The patient who suffered a pulmonary embolism was

Table 1. Demographics, operative indications, and operative procedures

	Average	Number
Age	38 yr	Range 16–62 yr
Sex		
Female	68%	15
Male	32%	7
Operative indications		
Refractory pain	100%	22/22
Recurrent chronic pancreatitis	14%	3/22
Suspected etiology		
Idiopathic	82%	18
Alcohol	9%	2
Post-ERCP	4.5%	1
Trauma	4.5%	1
Total	100%	22
Operative intervention	Previous operation	
Partial pancreatectomy (N = 3)	Subtotal pancreatectomy	1
	Pancreaticoduodenectomy	2
Completion pancreatectomy (N = 7)	Subtotal pancreatectomy	4
	Whipple operation	3
	Lateral pancreaticojejunostomy	2
Total pancreatectomy (N = 2)	Lateral pancreaticojejunostomy	2
Other operative interventions prior to pancreatectomy		
ERCP		17
Sphincterotomy/stent placement		7

treated with anticoagulants and recovered with no sequelae. The two patients with acute respiratory distress syndrome were treated with ventilatory and standard intensive care unit support, and both recovered. Minor complications included delayed gastric emptying (n = 6), urinary tract infection (n = 2), and one case each of pneumonia, hyperglycemia, wound infection, intra-abdominal hematoma, cellulitis, and line infection. Seven patients were discharged without any complications. There were no deaths in this series (Table 2).

Islet Cell Preparation and Transplantation and Metabolic Studies

The mean number of islet cell equivalents (IE) harvested was 245,457 (range 20,850 to 607,466 ± 175,234). The mean total number of islet cells isolated was 350,428 (range 31,500 to 1,164,000 ± 299,321). Following pancreatectomy and autologous islet cell transplantation, 41% of the patients (9 of 22) were insulin independent. These patients received an average of 4611 IE/kg (range 287 to 10,419). Of those patients who needed insulin at the time of discharge, 27% (6 of 22) required less than 10 units of NPH insulin per day (range 3

to 9 units/day). In this group of patients, 2802 IE/kg (range 218 to 5827) were transplanted. Finally, 32% (7 of 22) required an average of 25 units of insulin per day (range 15 to 40 units/day). These patients were transplanted with 2326 IE/kg (range 611 to 4593) (Table 3). Three of these seven patients were being treated for diabetes prior to their pancreatectomy and islet cell transplantation procedures.

Table 2. Major and minor complications

Complications	No. of Patients
Major	
Acute respiratory distress syndrome	2
Intra-abdominal abscess	1
Pulmonary embolism	1
Minor	
Delayed gastric emptying	6
Urinary tract infection	2
Pneumonia	1
Wound infection	1
Line infection	1
Hyperglycemia	1
Hematoma	1
Cellulitis	1

Table 3. Comparison of patients who are insulin independent vs. patients who are non-insulin independent

	Patients (N = 22)			
	Insulin independent		Non-insulin independent	
Etiology of pancreatitis				
Alcohol		1		1
Idiopathic		4		7
Idiopathic (pancreas divisum)		4		3
ERCP		0		1
Trauma induced		0		1
Total		9		13
Islet isolation numbers	Mean	Standard deviation	Mean	Standard deviation
Islet number*	475,126	(322,569)	264,098	(260,164)
Islet equivalents [†]	302,178	(185,459)	206,187	(163,475)
Islet equivalents per patient body weight transplanted [‡]	4,611	(3,180)	2,583	(1,859)

P values for *t* tests of mean differences:

* < 0.1242

† < 0.23

‡ < 0.11

None of the patients required hospitalization for acute metabolic consequences of diabetes after their surgery.

Five patients have completed both pre- and post-operative metabolic testing. Of these subjects, two were insulin independent postoperatively, whereas three required small amounts of long-acting insulin for glycemic control (average 12.7 units/day; range 6 to 22 units/day). On average, these subjects had normal glucose tolerance preoperatively (Fig. 1, A). Following pancreatectomy and islet autotransplantation, the glycemic response after glucose ingestion increased in these subjects, although one patient continued to have normal glucose tolerance. The C-peptide response to a bolus of intravenous arginine after surgery was decreased to approximately 38% ± 13% of the preoperative response, whereas C-peptide secretion after oral glucose was decreased to 59% ± 22% of the prepancreatectomy level (Fig. 1, B). All five subjects, including those requiring exogenous insulin, had demonstrable insulin and C-peptide secretion in response to intravenous and oral beta cell stimuli.

Pain Assessment

Although all patients were evaluated for quality of life by means of a modified version of the SF-36 and McGill questionnaires, at the present time complete data are available for 11 patients. Of these patients, seven were females and four were males. All identified unremitting abdominal pain as their primary presenting symptom (Table 4). Patients were interviewed at a median follow-up 19 months (range 3 to 41 months) after their procedures. The vast majority of

patients reported a significant decrease in frequency, duration, and intensity of pain, as well as a significant increase in quality of life since their procedures (Table 5).

Eighteen (82%) of the 22 patients who had resections are completely off narcotics. These patients required 78.4 (± 105.9) morphine equivalents (range 9 to 405) of pain medications preoperatively and only

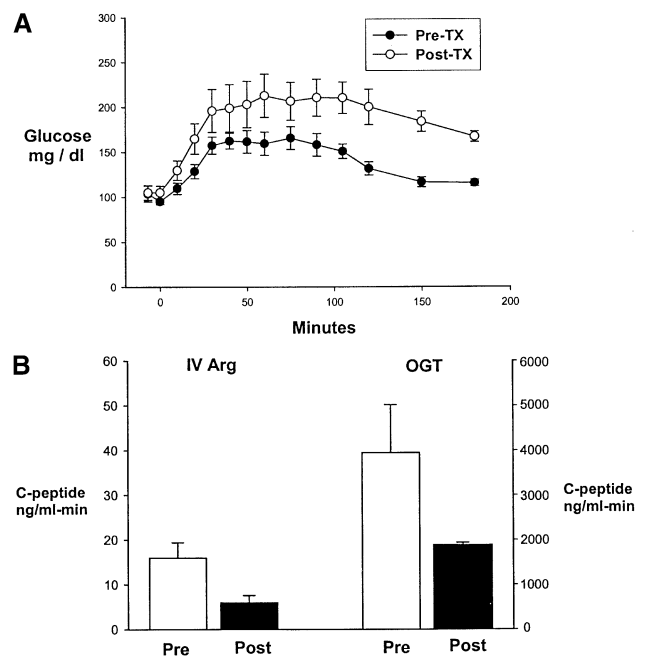


Fig. 1. Glucose tolerance test (A) and C-peptide secretion (B) in response to a bolus of intravenous arginine and oral glucose tolerance test before and after islet cell autotransplant in five patients undergoing pancreatectomy for unremitting pain from chronic pancreatitis.

Table 4. Demographics, presenting signs and symptoms, and medical history of patients who completed Pain Assessment and Quality of Life Questionnaires

	Study group (N = 11)	
	Number	Percentage
Age (median)	39.8 yr	
Sex		
Female	7	63.6%
Male	4	36.4%
Race/Ethnicity		
White	11	100%
Black	0	—
Other	0	—
Presenting signs and symptoms		
Abdominal pain	11	100%
Weight loss	2	18.2%
Nausea/vomiting	8	72.7%
Jaundice	0	—
Diarrhea	5	45.5%
Steatorrhea	1	9%
Fever/chills	0	—
Gastrointestinal bleeding	0	—
Past medical history		
Smoking	2	18.2%
Narcotic dependence	4	36.4%
Alcohol abuse	1	9%
Peptic ulcer disease	0	—
Hypertension	2	18.2%
Diabetes	2	18.2%
Myocardial infarction	0	—
Chronic obstructive pulmonary disease	0	—
Peripheral vascular disease	0	—
Presumed etiology of chronic pancreatitis		
Alcohol/drug induced	2	18.2%
Idiopathic	7	63.7%
Idiopathic (pancreas divisum)	2	18.2%
Trauma	0	—
Type of operation		
Total pancreatectomy	10	90.9%
Partial pancreatectomy	1	9%

9.5 (\pm 24) morphine equivalents (range 0 to 90) post-operatively. Three patients (13.6%) showed a 34% decrease in their narcotic requirement. Only one patient demonstrated an increase from 15 to 90 morphine equivalents in the narcotic requirement; this patient had a history of polysubstance abuse, which was not known preoperatively (Table 6).

DISCUSSION

Management of chronic pancreatitis presents a challenge to physicians.^{1,5,9,23,44,45} Although there remains no broad consensus as to the ideal treatment for

chronic pancreatitis, there is general agreement that for a subset of patients, primarily those who suffer from small duct pancreatitis, and those whose previous surgical procedures, medical management and more conservative surgical intervention did not produce desirable outcomes. In the past, near-total or total pancreatectomy has been avoided as a treatment option for these patients primarily because of concerns regarding increased morbidity associated with the surgery and fear of brittle diabetes. More recently, however, it has been shown that total pancreatectomy can be accomplished with acceptable morbidity and mortality.²⁰ One of the most relevant factors that precludes pancreatic resection as a desirable therapeutic option is the potential for surgically induced diabetes, which poses a very real threat of leaving patients with the unenviable choice of intractable pain vs. extremely difficult to manage diabetes. Immediate autotransplantation of islet cells after near-total to total pancreatectomy offers both the potential pain relief as well as a means of preserving endocrine function.

In this series the primary objective was to provide pain relief for patients followed by the secondary but equally important objective of preserving endocrine function.^{21,22,25,27,31,33,35,38,46} All of these patients presented with the primary symptom of refractory and unremitting pain, and three patients also had recurrent acute or chronic pancreatitis. The vast majority enjoyed dramatic and almost immediate relief of abdominal pain after their procedures, with 82% (n = 18) no longer requiring narcotics and 14% (n = 3) experiencing a marked decrease in the need for analgesics. Although the results are promising, this study represents a relatively short follow-up and cannot be used to draw definitive conclusions about long-term outcomes for this cohort of patients; clearly, further follow-up is required. Other groups have published their results comparing pain relief in patients undergoing pancreatectomy plus islet cell autotransplantation with a cohort of patients treated conventionally.^{47,48} It is now appropriate for such a comparison to be made in a randomized controlled trial.

In this series, after pancreatectomy, none of the patients presented with the brittle diabetes that is often seen in persons undergoing total pancreatectomy *without* islet cell transplantation.^{21,49} Forty-one percent of our patients are insulin free, 27% require less than 10 units per day of insulin, and the remaining seven patients require 15 to 40 units per day. Among the latter group, three of the patients were already receiving hypoglycemic agents and thus had antecedent diabetes as a result of either pancreatitis or concurrent type II diabetes. Closer analysis of these

Table 5. Results of McGill Pain Questionnaire

Item	Preoperative (N = 11)	Postoperative (N = 11)
Where is your pain?		
Internal (%)*	100	54.5
External (%)†	27.2	54.5
Pain rating index		
What does your pain feel like?		
Sensory (average)	19.4 ± 9.5	7.3 ± 6.6
Affective (average)	6.3 ± 3.9	0.9 ± 1.4
Evaluative (average)	4.2 ± 0.9	1 ± 1.3
Miscellaneous (average)	7.2 ± 2.1	1.2 ± 1.9
Pain-rating index total (average)‡	37 ± 13.4	11 ± 10.1
Present pain intensity (average)§	4.1 ± 0.8	0.7 ± 0.6
Number of words chosen (average)	13.3 ± 4.8	5.1 ± 4.4
How does your pain change with time?		
Continuous (%)	45.4	18.2
Steady (%)	18.2	9.1
Constant (%)	36.4	0
Rhythmic (%)	18.2	0
Periodic (%)	18.2	36.4
Intermittent (%)	27.3	9.1
Brief (%)	0	0
Momentary (%)	9.1	18.2
Transient (%)	27.3	18.2
How strong is your pain? (scale 1–5) 1 representing lowest and 5 representing highest		
At present (average)	4.1 ± 0.8	0.7 ± 0.6
At its worst (average)	5.0 ± 0	2.4 ± 2.2
At its least (average)	2.0 ± 0.8	1.2 ± 1.2
Worst toothache ever experienced (average)	4.3 ± 1	2.6 ± 2.3
Worst headache ever experienced (average)	4.5 ± 0.9	2.8 ± 2.4
Worst stomachache ever experienced (average)	4.4 ± 4.4	2.9 ± 2.5

* *t*-test showed $P < 0.01$.
 † *t*-test showed $P = 0.08$.
 ‡ *t*-test showed $P < 0.01$.
 § *t*-test showed $P < 0.01$.

results demonstrates that improved pancreatic endocrine function is associated with the transplantation of more islet cell equivalents per kilogram, with a desired minimum of 3,000 IE per kilogram.³⁶ The patients in our series who are now insulin independent each received more than 3000 IE/kg, which compares favorably with other larger series.^{32,35,36,38,47,50} Although there are many factors that affect the number and quality of islet cells isolated for transplantation, it is reasonable to conclude that the extent of pancreatic disease is one of these. This

raises the possibility that in many patients with unremitting pancreatitis, temporizing procedures such as the use of stents, partial resections, and drainage procedures ultimately cause more islet cell damage by prolonging the exposure to inflammation and fibrosis. In fact, it is interesting to speculate that many patients may benefit from early pancreatectomy with transplantation of a better-preserved islet mass. In our series patients who underwent a total pancreatectomy as the initial procedure had an average IE of 337, 888 + 142,577 and 4281 IE/kg, whereas patients who underwent completion pancreatectomy had an average IE of 209,546 + 177,952 and 3589 IE/kg. Based on previous reports of patients who underwent a partial pancreatic resection for chronic pancreatitis, 72% who required an 80% to 95% pancreatectomy developed diabetes, whereas only 32% of those receiving 80% resection became diabetic.⁵¹ Thus an important hypothesis for future consideration is that if pancreatic resection and islet cell autotransplantation were performed earlier in the course of treatment for chronic pancreatitis, islet cell function would be enhanced and rates of postoperative diabetes decreased. It seems likely that a major factor influencing beta cell function after pancreatectomy and islet cell autotransplantation is the severity of fibrosis.

Table 6. Pre- and postoperative morphine equivalent requirements

Patient	Preoperative	Postoperative
1	15	0
2	15	0
3	105	0
4	278	0
5	240	45
6	35	25
7	10	0
8	40	0
9	405	60
10	180	0
11	10	0
12	25	0
13	35	0
14	30	0
15	30	0
16	9	0
17	35	0
18	72	0
19	10	0
20	10	0
21	15	90
22	120	0
Average	78.4	9.5
SD	105.9	24

SD = standard deviation.

Simply put, a highly diseased pancreas will decrease the number and quality of islet cells available to transplant and therefore have a major impact on postoperative beta cell mass and glucose homeostasis.

In our series, although 68% of patients suffered complications, most of these complications were minor. None of the complications in our series were fatal, and they were similar to those in other series. Others have reported hepatic infarction, disseminated intravascular coagulation, splenic hemorrhage, and portal hypertension as being associated with intraportal infusion of islet cells.⁵²⁻⁵⁴ Another complication associated with this procedure is portal vein thrombosis. We have not experienced these complications in our series. Traditionally, portal vein thrombosis has been thought to be related to the volume of infused islet cells.^{55,56} More recently this concept has come under scrutiny, and there is now some debate over the most efficacious method of transplanting islet cells in terms of using a purified vs. an unpurified preparation. The use of unpurified preparations has the advantage of returning a larger mass of islet cells to the patient, thereby increasing the likelihood of improved metabolic function but increasing the risk of portal vein thrombosis.⁵⁷ Conversely, purified islet cell preparations reduce the volume of tissue infused and thus decrease the likelihood of portal vein thrombosis. However, with increased purification comes a decrease in the number and quality of these islet cells, as the gradients used for purification elicit a toxic effect on the islet cells.⁵⁸ Although in the past, portal vein thrombosis was thought to be related to the "final volume" infused, newer evidence suggests that tissue factor⁵⁹ released at the time of transplantation may be related to inducing a hypercoagulable state. In this series we used unpurified preparations to maximize the number and quality of islet cells and routinely administer heparin to these patients at the time of islet cell infusion.

Perhaps the primary limitation to the widespread application of autologous islet cell transplantation immediately after near-total to total pancreatic resection is that only a very limited number of facilities possess the expertise and technology to isolate and prepare pancreatic islet cells that are suitable for human transplantation. There are reports, however, demonstrating the feasibility of distance processing for both allo- and autoislets.^{60,61} The feasibility of this approach is enhanced by improvements in preservation methods, specifically by the development of the two-layer method,⁶² which allows for an extended preservation time in the ischemic pancreas, thereby increasing the islet cell yield and improving the viability of islet cells from suboptimal pancreata.⁶³ Although this method

still needs validation in a clinical autotransplant setting, preliminary results with alloislet transplantation are significant,⁶⁴⁻⁶⁶ and further studies should be pursued.

CONCLUSION

It has become increasingly clear during the past decade that islet cell autotransplantation is technically feasible. Short-term follow-up from our experience as well as long-term results from others demonstrate the feasibility of islet cell autotransplantation immediately after pancreatectomy as a means to alleviate pain from chronic pancreatitis and to prevent the development of surgically induced diabetes. As this technology improves, total pancreatectomy and autologous islet cell transplantation may become a standard therapy for patients suffering from refractory chronic pancreatitis.

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Discussion

Dr. M. Sarr (Rochester, MN): In the patients who had a partial reduction in their insulin dosage, did they have C-peptide in their blood?

Dr. H. Rilo: We are currently conducting a study with Dr. Dave D'Alessio, who has worked previously with Dr. Paul Robertson in Minnesota. We are testing the patients before and after transplantation. We have demonstrated that all resected and islet autotransplanted patients produce C-peptide.

Dr. Sarr: The question is, do they lack a total number of beta cells that is sufficient to lower their insulin level? In other words, did they have successful engraftment of the transplanted cells but just need to have more beta cells?

Dr. Rilo: Yes, a larger islet beta cell mass would be better. We see a decrease in the acute insulin response, and clearly there is a decrease in C-peptide that is evident on the arginine test and also on the oral glucose tolerance test.

Dr. L. Stewart (San Francisco, CA): Can you give me a better idea of what the preoperative opioid dose in these patients was across the board?

Also, what kinds of procedures had these patients had prior to your procedure, how many had a Puestow or a Whipple procedure, and so forth?

Dr. Rilo: Several of the patients had previous surgeries: seven had completion pancreatectomies, four had

subtotal pancreatectomies, two had pancreaticojejunostomies, and three had whipple procedures. These are often patients with long-standing disease who come to the Pancreatic Disease Center after having been referred by other surgeons and physicians; these patients have already gone through a sequence of stenting procedures, or have been exposed to drainage operations and resections before we complete the pancreatectomy and autotransplant.

As to your other question, we converted the doses to a morphine equivalent, because all of these patients, as you know, are taking an unaccountable amount of opioid analgesics. On average, the overall reduction was from 78 morphine equivalent requirements preoperatively to 9.5 postoperatively. Eighteen of the patients, representing 82% of the study population, no longer required narcotics.

Dr. A. Warshaw (Boston, MA): This is excellent work and clearly a major advance. I have one question and that is concerning the use of the insulin dosage to quantitate survival of the transplanted islets. People who are off of insulin entirely represent unequivocal success, but it is an observed fact, and also our experience, that patients after total pancreatectomy may require less insulin than those who still have some functional pancreas left because of the absence of glucagon production as well as insulin. So I am not sure that

the numerical insulin requirement is proportional to relative insulin independence or whether it is a valid measure of the success of the transplant.

Dr. Rilo: I am aware of the impaired gluco-regulation that is the result of the pancreatic glucagon deficiency, although there may be enteric sources of glucagon production present. I think this will be determined in the long term by the avoidance of complications. There is evidence that 50% of those patients who do not have any C-peptide will have a greater chance of developing complications. So the presence of a small amount of insulin being secreted will help to avoid those complications. We also see it in cases of so-called failed allotransplants where there is a very small amount of insulin and C-peptide being secreted, and those patients develop fewer complications. Although many patients with diabetes secondary to pancreatectomy take lower doses of insulin than individuals with type I diabetes, they almost always require multiple injections of mixed insulins daily. Many of our patients take only long-acting insulin and in smaller doses than is typical for pancreatic diabetes. We believe this is because of the preservation of some islet function.

Dr. T. Sielaff (Minneapolis, MN): We are obviously very interested in this sort of work and have been doing it since Drs. Sutherland and Najarian described it in the late 1970s.

Would you comment on the negative impact of previous surgery on islet yield and the effects of achieving insulin independence, and would you advocate this type of surgery for patients with idiopathic small duct chronic pancreatitis, similar to the presentation you were describing?

Dr. Rilo: I think that it will be one of the indications because the thinking is that if we can operate earlier, we can eventually preserve greater beta cell mass. We did an analysis of islet equivalence per gram of pancreas and islet equivalence per kilogram, and we clearly correlate the success with the amount of islets isolated per gram of pancreas. So if you eventually have more tissue, you will have greater success.

Dr. H. Reber (Los Angeles, CA): Your second conclusion indicates that you are recommending earlier surgical intervention, and I would like you to give us some sense of what you would recommend now with your experience.

Let's say that you have a patient who is 40 years of age and has idiopathic chronic pancreatitis. The patient does not have a dilated duct or diabetes. Would you suggest that a patient like that, with chronic recurrent intractable pain, go straight to total pancreatectomy and islet transplantation?

Dr. Rilo: These are patients that you say have failed—by that I mean they are left with intractable pain, correct?

Dr. Reber: Yes.

Dr. Rilo: Yes. I do not know of any resection that will improve their endocrine function, so why wait?

Dr. Reber: The patient is not diabetic.

Dr. Rilo: No, no, but I mean if we wait, we have nothing to offer that patient. The condition is likely to get worse and the patient's endocrine function will deteriorate. We do not really evaluate the deterioration of the islet cells as part of the process of cycles of inflammation. Clearly the islets are also affected.

Dr. C. Ulrich (Lewisville, TX): One of the things that I have been continuously approached about since the technology became available is for patients with hereditary pancreatitis, possibly to offer this to them in a setting where they are having recurrent episodes of acute pancreatitis; most investigators in the field believe that this probably needs to be done before they progress to advanced chronic pancreatitis because of the islet yield issue.

How long do you think it will be before this is ready for patients with hereditary pancreatitis, and is it really a viable option?

How many more years do we need to follow these patients to see how long the insulin independence lasts?

Dr. Rilo: The longest report in terms of a patient being free of insulin with autotransplantation comes from the Minnesota group and was published by Dr. Paul Robertson and that was more than 13 years ago, but this is just one case. Many improvements have been made with the procedure over the past several years.

First of all, we are now using a different collagenase that is called Liberase (Roche Applied Sciences, Indianapolis, IN). There are also new recombinant collagenases that look very promising, so we can perhaps improve the islet yield of these preparations. These new techniques will allow centers with greater experience in processing islets to receive a pancreas that has been resected at another center, by using the two-layer method with oxygenated perfluorocarbon, isolate and ship the islet preparation back to the center performing the pancreatectomy to be infused into the patient to prevent the development of diabetes. There are several centers now that are able to do that, and I think we are definitely one of those centers.

Dr. Ulrich: How many years do you think it will be before I have patients that come to me with recurrent acute pancreatitis, no obvious chronic pancreatitis, but they probably have low-grade chronic pancreatitis if they have recurrent acute disease, and this could actually be discussed with them by me as a viable option so that I could send them to Cincinnati or Minnesota or wherever? Next year, 2 years, 3 years, 5 years, is it ready now?

Dr. Rilo: It is ready now. I think the scientific community needs to come to an agreement.