Factors Associated with Insulin and Narcotic Independence after Islet Autotransplantation in Patients with Severe Chronic Pancreatitis

Syed A Ahmad, MD, Andrew M Lowy, MD, FACS, Curtis J Wray, MD, David D'Alessio, MD, Kywran A Choe, MD, Laura E James, MS, Andreas Gelrud, MD, Jeffrey B Matthews, MD, FACS, Horacio LR Rilo, MD

BACKGROUND: For patients who suffer from severe chronic pancreatitis, total pancreatectomy can alleviate pain, and islet autotransplantation (IAT) might preserve endocrine function and circumvent the complications of diabetes. Factors that determine success after this operation have not been clearly defined.

STUDY DESIGN: From 2000 to 2004, 45 total or subtotal pancreatectomies with IAT were performed. Patient characteristics, narcotic usage and insulin requirements were recorded at routine followup. Narcotic usage was standardized by conversion to morphine equivalents (MEs). Univariate and multivariate statistical analyses were performed to determine factors associated with insulin and narcotic independence.

RESULTS: Forty-five patients (30 women, 15 men), with a mean age of 39 years (range 16 to 62 years) underwent total or completion (n = 41) or subtotal (n = 4) pancreatectomies with IAT. Forty percent of patients were insulin free after a mean followup of 18 months (range 1 to 46 months). Factors associated in univariate analyses with insulin independence included female gender ($p = 0.004$), lower body weight (kg) ($p = 0.04$), more islet equivalents per kg body weight (IEQ/kg) transfused (<0.05), lower mean insulin requirement for the first 24 hours postoperation ($p = 0.002$), and lower mean insulin requirement at discharge ($p = 0.0005$). A multiple logistic regression using gender, body mass index, and IEQ/kg identified female gender as the only notable variable associated with insulin independence. There was a notable reduction ($p < 0.0001$) of postoperative MEs (mean 90 mg) compared with preoperative MEs (mean 206 mg) for the entire cohort; 58% of patients are narcotic independent. In the subset of patients with > 5 months followup (n = 32), 23 (72%) are narcotic free, with a substantial decrease in ME usage ($p = 0.01$).

CONCLUSIONS: The likelihood of glycemic control after IAT is related to both patient characteristics and islet cell mass. Based on these data, more islet cells may be required for insulin independence than previously thought. (J Am Coll Surg 2005;201:680–687. © 2005 by the American College of Surgeons)

Chronic pancreatitis (CP) is a disabling medical condition for which there is no highly effective medical therapy. Limited pancreatic resection can be an effective treatment for many patients with dominant strictures of the main pancreatic duct; unfortunately many patients suffer from CP in the absence of demonstrable main pancreatic duct pathology. [1-5] There are other patients who have minimal benefit or fail to respond to pancreatic resections or drainage procedures. These groups of patients may benefit from total pancreatectomy. This operation has traditionally been avoided because of the concerns of inducing brittle diabetes. With the advent of autologous islet autotransplantation, total pancreatectomy has emerged as

Competing Interests Declared: None.

Presented at the American College of Surgeons 90th Annual Clinical Congress, New Orleans, LA, October 2004.

Received October 14, 2004; Revised May 20, 2005; Accepted June 22, 2005.

From the Pancreatic Disease Center, Departments of Surgery (Ahmad, Lowy, Wray, James, Matthews, Rilo), Gastroenterology (Gelrud), Radiology (Choe), and Endocrinology (D'Alessio), University of Cincinnati, Cincinnati, OH.

Correspondence address: Syed A Ahmad, MD, Division of Surgical Oncology, Department of Surgery, University of Cincinnati College of Medicine, 234 Goodman St, ML 0772, Cincinnati, OH 45219.

ISSN 1072-7515/05/$30.00
doi:10.1016/j.jamcollsurg.2005.06.268

Abbreviations and Acronyms
BMI = body mass index
CP = chronic pancreatitis
IAT = islet autotransplantation
IEQ = islet equivalent
ME = morphine equivalent

a promising surgical paradigm in the treatment of unrelenting abdominal pain secondary to CP. [6-10]

Two common patient care concerns after IAT are the effectiveness in relieving chronic abdominal pain and postoperative glycemic control. Previously, we described the early results from our first 22 patients, in which 82% of patients experienced a marked reduction in chronic abdominal pain.[11] Forty-one percent of these initial patients remained insulin independent after IAT. From these preliminary findings, we suspected that multiple factors, both preoperative and postoperative, contribute to insulin independence. In this report we have analyzed our prospectively collected IAT database to identify prognostic factors associated with successful islet autotransplantation (IAT).

METHODS

Patients

All patient data in this study were collected and reported in strict compliance with patient confidentiality guidelines put forth by the University of Cincinnati Institutional Review Board. Between July 2000 and June 2004, the multidisciplinary Pancreatic Disease Center referred 45 patients for total or completion pancreatectomy with IAT. The diagnosis of CP was based on individualized characteristics of the patient's history, index operation, response to endoscopic stenting, laboratory tests, CT, ERCP, magnetic resonance cholangiopancreatography (MRCP), and final pathologic confirmation. For all patients the indication for surgery was intractable pain, and all used narcotics chronically for analgesia. All patients signed an informed consent document approved by the University of Cincinnati Institutional Review Board for the surgical procedure, IAT, and pre- and postoperative metabolic testing.

In preparation for surgery, all patients underwent CT scans, chest x-ray, metabolic testing, and preoperative anesthesia consultation. For patients requiring a splenectomy, vaccinations for *Hemophilus influenza* and Pneumoccocus were given.

Operative procedure

Intravenous antibiotic prophylaxis was given before the initial skin incision and was continued for 24 hours after the operation. Total pancreatectomy involved removing the entire pancreas, the spleen, the duodenum, and the distal common bile duct. Preservation of the pylorus was surgeon dependent. In some instances, the spleen was preserved. Gastrointestinal reconstruction involved either a side-to-side, two-layer gastrojejunostomy or an end-to-side duodenojejunostomy. An end-to-side hepaticojejunostomy proximal to the gastrojejunostomy usually restored bile duct continuity.

During the operation, blood supply to the pancreas was preserved for as long as possible 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; the remainder of the pancreas was mobilized and resected. Intravenous insulin drip was started immediately after pancreatic resection to maintain blood glucose levels less than 120 mg/dL. This was done to prevent glucose toxicity to islets because the detrimental effect of hyperglycemia on islet engraftment has been demonstrated in animal studies.[12] Finally, gastrostomy and jejunostomy tubes were placed at the discretion of the attending surgeon.

Postoperative care

Initial postoperative care was in the surgical intensive care unit. Serum glucose measurements were made hourly with a goal glucose < 120 mg/dL. To maintain glucose in this range, either a continuous insulin drip or intermittent insulin dose was administered by sliding scale protocol. Once patients were on a stable insulin schedule and off the insulin drip, they were transferred out of the ICU. On the surgical ward, glucose was carefully monitored by finger stick every 6 hours for 72 hours.

Islet transplantation

Islet cells were liberated from the remaining exocrine tissue using continuous cold enzymatic perfusion and digestion as described by Lee and colleagues.[13] 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 tem-

perature of the fluid was maintained close to 38°C to sustain optimum digestion. When digestion was completed (islets 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 diluting the islet containing solution and lowering its temperature to 7° to 10°C.

Approximately 4 hours after pancreas excision, the recovered islets were transplanted into the liver in one of two ways: either through a middle colic venous tributary or directly into the portal vein with a 16-gauge silicon catheter. Islet transplantation took place in the operating room while the patient remained under a general anesthetic. All patients received 5,000 IU IV heparin immediately preceding infusion of pancreatic islets. Portal venous pressure was selectively measured, dependent on islet cell load. Arterial and central venous pressures were monitored in all patients. Central venous pressures were monitored with an 18-gauge central line placed into the internal jugular or subclavian veins.

Medical records and statistical analysis

A retrospective review was undertaken to analyze factors that may predict insulin independence after IAT. The Pancreatic Disease Center database was queried for multiple demographic, clinical, and pathologic parameters. Summary and descriptive statistics were obtained using established methods. Continuous variables were summarized as mean ± SEM. Comparisons of continuous variables (age, weight, operative time, estimated blood loss, transfusion requirement, total volume of intraoperative IV fluids, islet equivalents [IEQ], body mass index [BMI = weight (kg)/(height —)^2], mean serum glucose < 24 hours after IAT, length of hospital stay, insulin requirement at discharge, followup insulin requirement, pre- and postoperative narcotic usage between insulin-independent and insulin-dependent patients were by Student's *t*-tests. Narcotic usage comparisons (pre- versus postoperative) were by paired *t*-test. Morphine equivalents (MEs) were calculated using the Narcotic Calculator software available at http://www.globalrph.com/narcotic_converter.htm. Comparisons of nominal data (gender, blood vessel used for islet injection, and etiology of CP) were by chi-square tests. A multiple logistic regression was used to identify variables independently associated with insulin independence. Data were analyzed using SAS statistical software (SAS version 8.1, SAS Institute Inc).

Table 1. Patient Demographics for 45 Patients Studied

Variables	Data
Mean age, y (range)	38 (16–62)
Mean weight, kg (range)	74 (39–110)
Mean body mass index (range)	26 (14–52)
Gender, n (%)	
Female	30 (67)
Male	15 (33)
Cause of pancreatitis, n (%)	
Idiopathic	39 (87)
Alcohol	2 (4)
Other	4 (9)
Previous pancreatic operation, n (%)	
Pancreaticoduodenectomy	10 (22)
Distal pancreatectomy	2 (4)
Lateral pancreaticojejunostomy	9 (20)
Operation, n (%)	
Partial pancreatectomy	4 (9)
Completion pancreatectomy	16 (35)
Total pancreatectomy	25 (56)

Body mass index = weight (kg)/[height(m)]^2.

RESULTS

Patients

From July 2000 to June 2004, 45 patients (30 women, 15 men), with a median age of 39 years (range 16 to 62 years) underwent total (n = 29), completion (n = 12), or near total (n = 4) pancreatectomies with IAT at the University of Cincinnati Medical Center (Table 1). In our series, the mean weight was 74 kg and BMI was 26. The etiology of CP was idiopathic (n = 39), alcohol (n = 2), trauma (n = 1), ERCP (n = 1), hereditary (n = 1), and drug toxicity (n = 1). Of the 39 patients with idiopathic CP, 8 were demonstrated to have pancreas divisum, and it remains unclear if the aberrant anatomy was the sole cause of CP in this subset of patients. One patient was insulin dependent before the pancreatectomy and IAT. Sixteen patients in this series had undergone previous pancreatic operations (five pancreaticoduodenectomies, four lateral pancreaticojejunostomies, two distal pancreatectomies, and five patients had both pancreaticoduodenectomies and lateral pancreaticojejunostomies).

Operation and complications

The mean operative time was 533 minutes (range 325 to 725 minutes), and there were no intraoperative deaths (Table 2). Intraoperative mean estimated blood loss was 563 mL (range 190 to 1,900 mL). Twenty-one patients

Table 2. Perioperative Factors

Perioperative factors	Insulin-dependent patients (n = 27)	Insulin-independent patients (n = 18)	p Value
Operating room time (min)	537 ± 20	525 ± 24	0.70
IV fluids (mL)	8,622 ± 627	8,211 ± 684	0.66
Estimated blood loss (mL)	563 ± 83	561 ± 120	0.98
Blood transfusion (U)	1.22 ± 0.3	1.78 ± 0.5	0.33
Initial 24-h serum glucose (g/dL)	126 ± 6	115 ± 4	0.13
Initial 24-h insulin (U)	32.6 ± 3.9	14.1 ± 3.8	0.002
Discharge insulin (U)	18.9 ± 2.9	5.7 ± 1.9	0.0005

p Values determined using Student's *t*-test. Data are presented as mean ± SEM.

did not require an intraoperative blood transfusion; 24 patients received a transfusion during the operation. The vessel selected for islet infusion was the middle colic vein in 33 patients, and the portal vein in 12 patients. Several perioperative factors were not associated with insulin dependence, including operative time, intraoperative IV fluids, mesenteric vessel used for islet infusion, estimated blood loss, and blood transfusion requirement.

There were several postoperative complications, including three deaths. One patient with known steatohepatitis died 6 months after IAT from fulminant hepatic failure. At autopsy, the liver was marked for fatty replacement and did not appear to be linked to islet cell-induced thrombosis. Another patient died 2 days after hospital discharge from a suspected narcotic overdose. The final patient death occurred 6 weeks postoperation from an apparent suicide. Four patients had delayed gastric emptying; each patient received enteral nutrition through a feeding jejunostomy tube. There were several thromboembolic complications (four cases of deep vein thrombosis and three cases of pulmonary embolism) requiring postoperative anticoagulation. There were three cases of both urinary tract infections and central line infections; this was most likely from prolonged Foley catheter and central venous line placement in the intensive care unit. There were three cases of symptomatic intraabdominal hematomas, two of which required emergent reoperation. There was one case each of the following complications: pneumonia, wound infection, intraabdominal abscess, pneumothorax, and neuropraxia.

Islet yield and insulin requirements

Forty-five patients underwent IAT at our institution, with 18 (40%) remaining insulin independent and 27 (60%) requiring insulin (Tables 3, 4). We identified several factors that might be related to insulin independence using univariate analysis. Patient gender was associated with insulin independence. Fifty-seven percent of female patients (17 of 30) are insulin free, in comparison with the number of male patients (1 of 15) insulin-free (chi-square $p = 0.001$). Weight (kg) was notably lower in patients remaining insulin independent (67.2 kg versus 78.6 kg, $p = 0.04$). BMI also might be an important prognostic factor, but was not statistically significant (insulin independent [24.2] versus insulin independent [27.9], $p = 0.06$).

In comparing insulin-free and insulin-requiring patients in univariate analysis, pancreas weight (kg) after harvest did not differ between groups ($p = 0.83$). The mean IEQ yield from the insulin-independent group (413,542) was higher than that from the insulin-dependent group (297,889), yet the variability among patients was such that this difference did not reach significance ($p = 0.19$). But the IEQ transfused per kg body weight (IEQ/kg) was considerable, again suggesting the importance of body weight. The insulin-independent patients had a markedly higher ratio (6,635 IEQ/kg) than the insulin-independent group (3,799 IEQ/kg) ($p = 0.04$).

All patients, as protocol after IAT, were transferred to the surgical intensive care unit for acute postoperative glucose management. Immediately after operation, virtually all patients required an insulin drip to maintain serum glucose < 120 mg/dL. The amount of insulin required in the initial 24 hours postoperation was considerably lower in the insulin-independent patients (14.1 U) than in the insulin-dependent group (32.6 U, $p = 0.002$). For all study patients, the mean serum glucose in the initial 24 hours tended to be lower in patients who remained insulin independent than in those requiring insulin (115 mg/dL versus 126 mg/dL) in the initial 24 hours after IAT, but this difference was not statistically significant ($p = 0.13$, Table 2).

Of the patients who are now insulin independent,

Table 3. Islet Yield and Body Weight Factors

Variables	Insulin-dependent patients (n = 27)	Insulin-independent patients (n = 18)	p Value
Gender			
Male (n = 15)	14	1	
Female (n = 30)	13	17	0.001
Mean weight (kg)	78.6 ± 3.2	67.2 ± 4.1	0.04
Body mass index*	27.9 ± 1.5	24.2 ± 1.3	0.06
Pancreas weight (g)*	66.3 ± 8.1	64.1 ± 6.2	0.83
IEQ, mean	297,889 ± 49,480	413,542 ± 70,985	0.19
IEQ/pancreas weight (g)*	5,025 ± 968	7,304 ± 1,722	0.24
IEQ/body weight (kg)*	3,799 (±629)	6,635 (±229)	0.04
IEQ/body mass index*	11,258 (±1,964)	17,590 (±3,139)	0.09

Gender statistical differences determined by chi-square analysis. All other variables compared using Student's *t*-test.
*Data are presented as mean ± SEM.
IEQ, islet equivalents.

most required small amounts of insulin to treat intermittent hyperglycemia at the time of discharge from the hospital. Insulin-independent patients required less insulin (5.7 U/24 h) compared with insulin-dependent patients (18.9 U/24 h) ($p = 0.0005$). Insulin-independent patients had a longer length of hospital stay (15 days versus 11 days, $p = 0.05$).

A multiple logistic regression was used to analyze several variables (gender, BMI, and IEQ/kg) for their association with subsequent insulin independence in all 45 patients. Gender was the only variable that appeared to be associated with insulin independence ($p = 0.013$; odds ratio = 16.24 ± 0.733).

Narcotic requirements

In this series, the mean preoperative narcotic usage in MEs was 206.1 mg (range 10 to 1,120 MEs) (Table 5). The postoperative ME usage for this same group of patients was 90.0 mg (range 0 to 520 mg), a marked reduction ($p < 0.0001$ by paired *t*-test) of narcotic requirements. Twenty-six patients (58%) had a notable reduction in chronic abdominal pain as demonstrated by narcotic independence at last followup. Of the first 32 patients, with a mean followup of 23 months (range 7 to 54 months), patients who could not be weaned from their narcotics required a greater amount preoperatively when compared with patients who were narcotic independent (167 mg versus 48 mg, $p = 0.01$).

Table 4. Insulin Requirements

	All patients (n = 45)	
Insulin requirement (U/d)	n	%
0	18	40
1–20	11	24
20–40	9	20
> 40	7	16

DISCUSSION

CP is a progressive inflammatory process that causes permanent damage to both the exocrine and endocrine pancreas. This process often impairs insulin secretory function, and insulin-dependent diabetes evolves in 20% to 30% of all patients with CP.[14] Most patients are treated initially with a combination of narcotics and endoscopic interventions. Unfortunately, greater than 50% develop progressive symptoms and require additional interventions.[15] For these patients, several surgical options are available. When patients have localized disease or dominant strictures in the main pancreatic duct, resection often can be performed. Patients with sufficiently dilated ducts usually undergo a decompressive operation. Although these operations can provide long-term pain relief for more than 50% of these patients, they are associated with a 30% to 50% incidence of postsurgical diabetes in patients undergoing partial re-

Table 5. Pre- and Postoperative Narcotic Usage in All Patients

Patients (n = 45)	Preoperative MEs, mean (range)	Postoperative MEs, mean (range)	p Value
All patients	206 (0–1,120)	90 (0–520)	0.005
Initial 32 patients	168 (0–1,120)	45 (0–490)	0.01
Last 13 patients	300 (117–1,080)	200 (0–520)	0.26

p Value determined by Student's *t*-test.
MEs, morphine equivalents.

section and nearly 100% incidence in patients undergoing near-total or total pancreatectomy.[16,17] The resulting diabetes is difficult to control and can be associated with life-threatening episodes of hypoglycemia.[18]

With the advent of autologous IAT, surgeons are now performing near-total or total pancreatectomy to treat patients who suffer from CP, and those whose previous surgical and medical management method did not produce desirable outcomes. In our initial report of 22 patients undergoing IAT at the University of Cincinnati, 41% of patients were insulin independent and 82% were weaned off all narcotics.[11] Since that report, we have performed an additional 23 total or completion pancreatectomies with IAT. During this time, it became clear to us that the likelihood of glycemic control after IAT is related to both patient characteristics and islet cell mass. With this in mind, we have reviewed our prospective database to identify factors associated with insulin independence.

In this updated series, 40% of patients remained insulin independent. Patients who remained insulin independent had a markedly increased number of islets transplanted relative to patient body weight (IEQ/kg). Patients receiving at least 6,635 IEQ/kg were more likely to be insulin independent when compared with patients who received transplantations of a smaller number. These results differ from the two largest series published to date. Gruessner and colleagues[19] recently updated the results of the University of Minnesota experience. In this large series, 112 patients with CP underwent total pancreatectomy and IAT. Thirty-nine percent of patients remained insulin independent, and the Minnesota group found that transplantation of more than 2,500 IEQ/kg was associated with a chance of becoming insulin independent. In this subset of patients, 72% became completely and 14% partially insulin independent. These results contradict those in a series reported by Clayton and colleagues[20] documenting the Leicester General Hospital experience. In this report, the authors found no relationship between number of the islets transplanted and insulin independence. Our results are similar to those in the Minnesota experience, in which an association between islet number and insulin independence was found. But in our series, a greater total number of islets were necessary (6,635 IEQ/kg [Cincinnati] versus 2,500 IEQ/kg [Minnesota]). Our series of patients was similar to the Leicester series, in which a greater proportion of patients (91%) underwent total or completion pancreatectomy. In contrast, many patients underwent subtotal pancreatectomy in the Minnesota series, allowing for endogenous production of insulin by the remaining pancreas. The decreased number of islets harvested, in the Leicester series (2,020 IEQ/kg) might explain why no correlation was demonstrated between islet number and insulin independence. A review of the International Islet Transplant Registry (n = 140) indicated that 3,000 IEQ/kg are necessary for insulin independence, although some of the reported patients have no followup after 1 year.[18]

We also found a direct association between patient body weight and insulin independence, indicating that patient selection might also contribute to the success of islet transplantation. In this series, patients with an absolute weight of 78 kg or a BMI greater than 28 appeared to have an increased chance of requiring longterm insulin supplementation. Even though this finding is not surprising, no previous studies have reported this association. The relationship between insulin resistance and obesity has been well documented.[21] It also has been shown that after IAT, timing of the plasma insulin responses to both glucose and arginine are normal, but the magnitudes of the responses are less than normal.[22] So after IAT, the decreased number of functioning islets is less able to compensate for insulin resistance, and abnormalities in glucose tolerance ensue. This combination might prevent patients with an increased BMI from becoming insulin independent. Finally, it also has been demonstrated that weight loss is associated with an increase in insulin secretion.[23] In our series, one patient with a preoperative BMI of 33 required insulin postoperatively for glycemic control, but became insulin independent once she lost weight. We would suggest that patients with a BMI greater than 30 be counseled to lose weight before IAT.

Critical analysis of our data demonstrates that early graft function, in the first 24 hours, may predict the longterm likelihood of insulin independence. This is supported by the fact that patients requiring less than 15 U of insulin during the first 24 hours had a higher rate of insulin dependence. Although the mean blood glucose in the first 24 hours was not associated with longterm success, it has been demonstrated in preclinical models that hyperglycemia can cause β-cell toxicity.[24] So it is possible that patients with poorly controlled blood sugars could have experienced hyperglycemia-induced apoptosis of the transplanted islets. It is now our practice

to routinely administer trophic doses of IV insulin (0.5 to 1 U/h) to all patients during the first 24 hours postoperation. This practice is supported by studies that demonstrate the effects of exogenous insulin in slowing islet exhaustion and chronic overstimulation in recipients with marginal islet mass.[6,7] Whether more extended periods of intensive insulin therapy would provide additional benefit for islet autographs function is a matter that will need careful investigation.

In this series, a history of previous pancreatic surgery was not directly associated with insulin dependence. It did, however, predict islet yield. Patients undergoing a total pancreatectomy (n = 29) had the highest islet yield per kg body weight (5,482 IEQ/kg body weight); the next highest yield was found in patients who had previously undergone only a distal pancreatectomy (n = 5, 4,642 IEQ/kg body weight). The lowest yield was found in patients who had previously undergone a Puestow procedure (n = 4, 1,924 IEQ/kg body weight). A similar pattern was demonstrated by the Minnesota group, who demonstrated the negative impact of a Puestow procedure on islet yield.[19] Ultimately, many factors determine the number of islets isolated including degree of fibrosis, ischemia of the resected pancreas, and inability to distend the pancreas duct (ie, Puestow procedure) during the digestion process. So performing IAT earlier in the treatment algorithm might lead to a higher success rate by treating patients who have not undergone previous interventions and have less parenchymal fibrosis.

An unexpected finding in this study was the large discrepancy between male and female insulin requirements after IAT. Of the 18 patients who were insulin free, 17 were women. To the best of our knowledge, this is the first report of an association between gender and insulin independence. A multiple logistic regression including gender, BMI, and IEQ/kg found gender to be an important independent variable ($p = 0.013$). One explanation for this finding could simply be the observed islet yield and weight differences. Women had a higher islet yield than men (5,655 IEQ/kg versus 3,488 IEQ/kg, $p = 0.07$), yet this was not substantial. In this series, men were, on average, 10 kg heavier than women (81.9 kg versus 70.1 kg, $p = 0.02$). But there were no statistical gender differences ($p = 0.75$) with regard to BMI (men, 26.9 and women, 26.2). These gender data need to be interpreted carefully, and perhaps as our sample size increases, the importance of gender will be easier to explain.

Finally, we analyzed factors associated with narcotic independence after operation. Overall, there was a marked reduction ($p < 0.005$) of preoperative MEs (206 mg, range 0 to 1,120 mg) versus postoperative MEs (90 mg, range 0 to 520 mg); 58% (n = 26) had a notable reduction in chronic abdominal pain as demonstrated by narcotic independence. In this updated analysis, there was no difference in preoperative narcotic dose between narcotic-independent and -dependent patients. But this updated experience included 13 patients with a mean followup of less than 5 months (range 1 to 7 months). If we analyze the first 32 patients, with a mean followup greater than 22 months (range 7 to 54 months), patients who could not be weaned from their narcotics required a greater amount preoperatively when compared with patients who were narcotic independent (167 mg versus 48 mg, $p < 0.05$). This is not surprising because most patients require upwards of 6 to 7 months after their operation to be weaned from their narcotics.

Based on our experience, total pancreatectomy is an effective modality in alleviating intractable pain caused by CP. In the past, this operation was avoided because of the fear of inducing labile diabetes. Our experience demonstrated that IAT may offer some patients the chance for insulin independence. Our results indicated that a greater total number of islets may be necessary to achieve glycemic control than previously thought. So operating earlier in the disease course before the islets are destroyed might improve the results of this procedure. Patient selection also is important; patients with increased BMI are less likely to benefit from this operation and should be counseled to lose weight before IAT. This operation may become more commonplace in treating patients with intractable CP; as our understanding of factors predicting successful outcomes after IAT improves.

Author Contributions

Study conception and design: Ahmad, Wray, Rilo
Acquisition of data: Lowy, Wray, D'Allesio, Choe, Matthews
Analysis and interpretation: Ahmad, Wray, Rilo
Drafting of manuscript: Ahmad, Wray
Critical revision: Lowy, D'Allesio, Gelrud, Matthews, Rilo
Statistical analysis: James

Acknowledgment: We wish to thank Kate Trulock and Debbie Soldano for collecting information and data for this study.

REFERENCES

1. Izbicki JR, Bloechle C, Knoefel WT, et al. Surgical treatment of chronic pancreatitis and quality of life after operation. Surg Clin North Am 1999;79:913–944.
2. Traverso LW, Kozarek RA. Pancreatoduodenectomy for chronic pancreatitis: anatomic selection criteria and subsequent long-term outcome analysis. Ann Surg 1997;226:429–435; discussion 435–438.
3. Hutchins RR, Hart RS, Pacifico M, et al. Long-term results of distal pancreatectomy for chronic pancreatitis in 90 patients. Ann Surg 2002;236:612–618.
4. Cooperman AM. Surgery and chronic pancreatitis. Surg Clin North Am 2001;81:431–455.
5. Izbicki JR, Bloechle C, Broering DC, et al. Extended drainage versus resection in surgery for chronic pancreatitis: a prospective randomized trial comparing the longitudinal pancreaticojejunostomy combined with local pancreatic head excision with the pylorus-preserving pancreatoduodenectomy. Ann Surg 1998; 228:771–779.
6. Farney AC, Najarian JS, Nakhleh RE, et al. Autotransplantation of dispersed pancreatic islet tissue combined with total or near-total pancreatectomy for treatment of chronic pancreatitis. Surgery 1991;110:427–437; discussion 437–439.
7. White SA, Davies JE, Pollard C, et al. Pancreas resection and islet autotransplantation for end-stage chronic pancreatitis. Ann Surg 2001;233:423–431.
8. Wahoff DC, Papalois BE, Najarian JS, et al. Autologous islet transplantation to prevent diabetes after pancreatic resection. Ann Surg 1995;222:562–575; discussion 575–579.
9. White SA, London NJ, Johnson PR, et al. The risks of total pancreatectomy and splenic islet autotransplantation. Cell Transplant 2000;9:19–24.
10. Rilo HL, Carroll PB, Tzakis A, et al. Insulin independence for 58 months following pancreatic islet cell transplantation in a patient undergoing upper abdominal exenteration. Transplant Proc 1995;27:3164–3165.
11. Rodriguez Rilo HL, Ahmad SA, D'Alessio D, et al. Total pancreatectomy and autologous islet cell transplantation as a means to treat severe chronic pancreatitis. J Gastrointest Surg 2003;7:978–989.
12. Merino JF, Nacher V, Raurell M, et al. Optimal insulin treatment in syngeneic islet transplantation. Cell Transplant 2000; 9:11–18.
13. Lee TC, Barshes NR, Brunicardi FC, et al. Procurement of the human pancreas for pancreatic islet transplantation. Transplantation 2004;78:481–483.
14. Rossi RL, Rothschild J, Braasch JW, et al. Pancreatoduodenectomy in the management of chronic pancreatitis. Arch Surg 1987;122:416–420.
15. Buscher HC, Jansen JB, van Dongen R, et al. Long-term results of bilateral thoracoscopic splanchnicectomy in patients with chronic pancreatitis. Br J Surg 2002;89:158–162.
16. Somogyi L, Forsmark CE. Pancreatic duct stenting in benign pancreatic disease. Semin Gastrointest Dis 1998;9:73–79.
17. Slezak LA, Andersen DK. Pancreatic resection: effects on glucose metabolism. World J Surg 2001;25:452–460.
18. Panaro F, Testa G, Bogetti D, et al. Auto-islet transplantation after pancreatectomy. Expert Opin Biol Ther 2003;3:207–214.
19. Gruessner RW, Sutherland DE, Dunn DL, et al. Transplant options for patients undergoing total pancreatectomy for chronic pancreatitis. J Am Coll Surg 2004;198:559–567; discussion 568–569.
20. Clayton HA, Davies JE, Pollard CA, et al. Pancreatectomy with islet autotransplantation for the treatment of severe chronic pancreatitis: the first 40 patients at the Leicester General Hospital. Transplantation 2003;76:92–98.
21. Frezza EE. Are we closer to finding the treatment for type 2 diabetes mellitus in morbid obesity? Are the incretins the key to success? Obes Surg 2004;14:999–1005.
22. Pyzdrowski KL, Kendall DM, Halter JB, et al. Preserved insulin secretion and insulin independence in recipients of islet autografts. N Engl J Med 1992;327:220–226.
23. Yoshida Y, Hashimoto N, Tokuyama Y, et al. Effects of weight loss in obese subjects with normal fasting plasma glucose or impaired glucose tolerance on insulin release and insulin resistance according to a minimal model analysis. Metabolism 2004; 53:1095–1100.
24. Korsgren O, Jansson L, Sandler S, et al. Hyperglycemia-induced B cell toxicity. The fate of pancreatic islets transplanted into diabetic mice is dependent on their genetic background. J Clin Invest 1990;86:2161–2168.