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-