Quality of Life Improves for Pediatric Patients After Total Pancreatectomy and Islet Autotransplant for Chronic Pancreatitis

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BACKGROUND & AIMS: Total pancreatectomy (TP) and islet autotransplant (IAT) have been used to treat patients with painful chronic pancreatitis. Initial studies indicated that most patients experienced significant pain relief, but there were few validated measures of quality of life. We investigated whether health-related quality of life improved among pediatric patients undergoing TP/IAT. **METHODS:** Nineteen consecutive children (aged 5–18 years) undergoing TP/IAT from December 2006 to December 2009 at the University of Minnesota completed the Medical Outcomes Study 36-item Short Form (SF-36) health questionnaire before and after surgery. Insulin requirements were recorded. **RESULTS:** Before TP/IAT, patients had below average health-related quality of life, based on data from the Medical Outcomes Study SF-36; they had a mean physical component summary (PCS) score of 30 and mental component summary (MCS) score of 34 (2 and 1.5 standard deviations, respectively, below the mean for the US population). By 1 year after surgery, PCS and MCS scores improved to 50 and 46, respectively (global effect, PCS $P < .001$, MCS $P = .06$). Mean scores improved for all 8 component subscales. More than 60% of IAT recipients were insulin independent or required minimal insulin. Patients with prior surgical drainage procedures (Puestow) had lower yields of islets ($P = .01$) and greater incidence of insulin dependence ($P = .04$). **CONCLUSIONS: Quality of life (physical and emotional components) significantly improve after TP/IAT in subsets of pediatric patients with severe chronic pancreatitis. Minimal or no insulin was required for most patients, although islet yield was reduced in patients with previous surgical drainage operations.**

Keywords: Pancreas; Inflammation; Therapy; Clinical Trial.

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Chronic pancreatitis (CP), though rare in childhood, can result in significant morbidity. In children, disease results most commonly from genetic mutations or unknown causes.[1,2] Affected children generally present with abdominal pain, with or without elevation of serum amylase, lipase, or conventional imaging evidence of pancreatitis. The disease is usually progressive, with increasing pain and narcotic dependence, potential progression to exocrine and endocrine insufficiency, and an elevated lifetime risk for pancreatic adenocarcinoma.[3] CP is associated with significant decrements in health-related quality of life (HRQOL) in adults,[4–7] but the pediatric literature is sparse.

Treatment, directed at relieving pain and restoring quality of life, may include narcotic analgesics, pancreatic enzymes to reduce pancreatic stimulation, antioxidants, celiac plexus blocks, and endoscopic duct decompression.[8–11] Patients who fail these medical and endoscopic interventions or remain narcotic dependent may be candidates for surgical intervention. Although partial resections (distal pancreatectomy or proximal [Whipple] pancreaticoduodenectomy), drainage operations such as pancreaticojejunostomy (Puestow), or variants (Frey, Beger) are considered standard surgical care, pain may not resolve, or eventually relapse in up to 50% of patients, often with progression to exocrine and endocrine insufficiency.[12,13] Drainage operations do not reduce the risk for developing adenocarcinoma in the residual pancreas, a lifetime risk which may exceed 40% with hereditary pancreatitis.[3] Total pancreatectomy removes the entire pancreas and thus the cause of pain and presumably cancer risk, but by itself results in brittle surgical diabetes, and therefore is rarely performed for CP. A novel approach, first described in 1977, is to isolate the patient's own islets at the time of pancreatectomy and autotransplant the islets into the portal vein.[14] They engraft in the liver and secrete insulin in response to glucose, without any need for immunosuppression.[15]

Although total pancreatectomy (TP) and islet autotransplantation (IAT) has the potential to relieve pain while preserving insulin secretion, few centers have experience with this technique, with only 3 worldwide reporting more than 50 cases.[16] The bulk of experience with TP/IAT has been in adults. Overall, more than half of patients successfully wean off narcotic medications.[17–21] At experienced institutions, insulin independence rates range from 26% to 41%.[17,22–24] In addition, another third of patients require minimal insulin to maintain euglycemia.[15,25] Data are limited for pediatric patients. Retrospective studies suggest that the majority have complete or significant pain relief, and half are insulin independent at 1 year.[26] Objective measures of HRQOL are lacking.

Abbreviations used in this paper: CP, chronic pancreatitis; HbA, hemoglobin A; HRQOL, health-related quality of life; IAT, islet autotransplant; IE, islet equivalent; MCS, mental component summary; PCS, physical component summary; SF-36, 36-Item Short Form Medical Outcomes Survey; TP, total pancreatectomy.

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The primary aim of the current study was to prospectively determine if HRQOL is improved in pediatric patients undergoing TP/IAT, using a standardized health status measure. The secondary aims were to prospectively follow narcotic requirements and islet function.

Methods

Subjects

Nineteen consecutive pediatric patients (≤18 years old) scheduled for TP/IAT between December 2006 and December 2009 at the University of Minnesota Amplatz Children's Hospital were enrolled in a prospective cohort evaluating HRQOL, narcotic use, and insulin requirements. All had a diagnosis of CP or acute relapsing pancreatitis confirmed by gastroenterologists with a specialty focus in pancreatic diseases, and had failed medical and/or endoscopic treatment. The diagnosis of CP was based on clinical history and imaging evidence (calcifications on computerized tomography [CT] scan, ductal abnormalities on magnetic resonance cholangiopancreatogram or endoscopic retrograde cholangiopancreatogram, and/or endoscopic ultrasound findings), and in many cases was supported by positive genetic testing for hereditary pancreatitis (PRSS1 gene mutations). Since 2008, all patients were evaluated by a multidisciplinary team, including surgeons, gastroenterologists, and endocrinologists; those meeting criteria in Table 1 were considered candidates for surgery.

One patient (#12) had pre-existing insulin-dependent diabetes secondary to CP, but was C-peptide positive (indicating functioning beta cells), and thus underwent an IAT to preserve residual beta cell mass. One (#10) did not receive the planned IAT because islet yield was insufficient.

The study protocol was approved by the University of Minnesota Institutional Review Board. Informed consent and assent (where applicable) were obtained for all participants.

Table 1. University of Minnesota Criteria for TP/IAT[a]

Patient Must Fulfill Criteria Numbers 1–5:

1. Diagnosis of chronic pancreatitis, based on chronic abdominal pain of >6 mo duration and at least 1 of the following:
   - Pancreatic calcifications on computerized tomography scan.
   - At least 2 of the following: ≥4/9 criteria on EUS, compatible ductal or parenchymal abnormalities on secretin MCRP; abnormal endoscopic pancreatic function tests (peak HCO_2 ≤80 mmol/L)
   - Histopathology confirmed diagnosis of chronic pancreatitis
   - Compatible clinical history and documented hereditary pancreatitis (PRSS1 gene mutation)
   - History of recurrent acute pancreatitis (more than 1 episode of characteristic pain associated with imaging diagnostic of acute pancreatitis and/or elevated serum amylase or lipase >3 times upper limit of normal)
2. At least 1 of the following:
   - Daily narcotic dependence
   - Pain resulting in impaired quality of life, which may include: inability to attend school, recurrent hospitalizations, or inability to participate in usual, age-appropriate activities
3. Complete evaluation with no reversible cause of pancreatitis present or untreated
4. Failure to respond to maximal medical and endoscopic therapy
5. Adequate islet cell function (nondiabetic or C-peptide positive)[b]

EUS, endoscopic ultrasound; MCRP, magnetic resonance cholangiopancreatogram.

[a]Criteria were formally implemented in 2008.

[b]Patients with C-peptide negative diabetes meeting criteria 1 through 4 are candidates for TP alone.

Surgical Procedure and Islet Isolation

The TP was done with a pylorus-sparing segmental duodenectomy in most cases, with reconstruction via a duodenoenterostomy, and, usually, an adjacent choledochoenterostomy. Islet isolation and purification was performed in the University of Minnesota Molecular and Cellular Therapeutics Good Manufacturing Practice facility, as previously described.[15,27] Briefly, the pancreas was distended with cold enzyme solution (SERVA Electrophoresis GmbH, Heidelberg, Germany)[28] using a pressure-controlled pump system,[29] and then digested using the semiautomated method of Ricordi.[30] The islets were purified by continuous iodixanol (OptiPrep, Axis-Shield, Oslo, Norway) density gradient on a COBE 2991 cell separator (Gambro BCT, Lakewood, CO, USA)[31] only if the total digest volume was large (> approximately 20 mL). The number of islets were quantified as islet equivalents (IE), which is islet mass standardized to an islet size of 150 μm diameter.

The islet preparation was infused into the portal system after surgical enteric-biliary reconstruction and before closure of the laparotomy incision. In most cases, the splenic vein stump was cannulated proximal to its termination in the portal vein; alternatives include direct puncture of the portal vein or cannulation of the umbilical vein. If the portal pressures elevated to ≥25–30 cm H_2O, the infusion was stopped. In 16 cases, all islets were infused intraportally. In 2 cases (#6 and #8), a majority were infused intraportally, with a portion infused into the peritoneal cavity due to elevated portal pressures.[15]

HRQOL Assessments

Patients (with assistance of parents) were asked to complete comprehensive survey instruments before surgery and at 3, 6, and 12 months, and annually after surgery. Baseline surveys were administered in the clinic at the preoperative visit (within 1 week of surgery). Subsequent follow-up surveys were mailed to patients and returned by mail or at follow-up visits. All patients completed at least 1 follow-up survey. Fifty surveys were available. The Medical Outcomes Study (MOS) 36-item Short Form (SF-36) Health Survey was used as a measure of generic HRQOL.[32–33] The SF-36 gives a health status profile along 8 dimensions corresponding to the following scale scores: physical functioning, role limitations attributed to physical health problems, bodily pain, general health, social functioning, vitality, role limitations attributed to emotional health problems, and mental health. The scale scores range between 0 and 100 with higher values signifying more positive health attributes. These 8 scale scores are the basis of the Physical Component Summary (PCS) and the Mental Component Summary Scale (MCS) scores. These latter more global measures are standard normalized (mean of 50, standard deviation of 10) to a representative sample of the United States. Additional survey items included questions about pain symptoms, narcotic use, and insulin requirements.