The American Journal of Surgery xxx (2016) 1–7

Contents lists available at ScienceDirect

The American Journal of Surgery

journal homepage: www.ajconline.org

Clinical effectiveness of a pylorus-preserving procedure on total pancreatectomy with islet autotransplantation

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ARTICLE INFO

Article history:
Received 24 June 2016
Received in revised form
7 September 2016
Accepted 12 September 2016

Keywords:
Total pancreatectomy
Islet autotransplantation
Chronic pancreatitis
Pylorus preservation

ABSTRACT

Background: The impact of pylorus preserving procedures (PP) on total pancreatectomy with islet autotransplantation (TPIAT) has not been examined. This study aimed to investigate the clinical impact of the PP on TPIAT.

Methods: The Baylor Simmons Transplant Institute database was queried to identify seventy-three patients who underwent TPIAT from 2006 to 2014. All patients were investigated in postoperative complications, long-term nutritional status, and graft function.

Results: Patients with PP did not face worse outcomes in terms of delayed gastric emptying and length of hospital stay. Also, nutritional status and metabolic outcome, such as body weight, serum albumin level, serum vitamin level, HbA1c level, graft survival rate and insulin independent rate, were similar between both groups.

Conclusions: Clinical results including the graft function indicated that patients undergoing TPIAT with PP did not amplify surgical complications such as delayed gastric emptying and showed no significant advantage of nutrition and metabolic outcome.

1. Introduction

Total pancreatectomy with islet autotransplantation (TPIAT) is a promising treatment option for patients with refractory chronic pancreatitis (CP).[1] Since its introduction into clinical practice several decades ago, TPIAT has been refined to help improve the quality of life and postsurgical narcotic dependency of patients.[2,3] During the last decade, progress in the procedure has led to TPIAT being increasingly used as a treatment option for CP patients at more transplant centers.[4,5]

TPIAT is a complex and invasive procedure associated with high morbidity and mortality rates.[6] Pancreaticoduodenectomy (PD) and reconstruction of the digestive tract during total pancreatectomy (TP) are associated with certain surgical complications. Historically, the Whipple procedure, including distal gastrectomy, has been the standard procedure for removing neoplasms located in the head of the pancreas.[7] In order to reduce marginal ulceration and improve postoperative nutritional status, Traverso and Longmire suggested resorting to the pylorus-preserving pancreatoduodenectomy (PPPD) procedure.[8] However, clinical trials revealed that preservation of the pylorus led to worse early postoperative outcomes, especially in terms of delayed gastric emptying (DGE), and that long-term patient benefits were less than expected.[9,10] Hence, the procedure to remove the pylorus ring has been increasingly used during PD for oncological surgeries. However, studies examining pylorus preservation have not involved TPIAT patients.

TPIAT is clearly different from other pancreatic resection procedures such as pancreaticoduodenectomy and distal pancreatectomy in terms of surgical complications, the loss of pancreatic exocrine function, and posttransplant glycemic control. In theory, TP does not present complications of pancreatic fistula, which is one of the most severe complications in pancreatic resection and a

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http://dx.doi.org/10.1016/j.amjsurg.2016.09.051
0002-9610/

cause of DGE. Additionally, TP results in a complete loss of exocrine function in the pancreas; hence, nutritional status will be significantly altered. In general, the isolated islets are infused into the portal vein, and the procedure as a whole affects the portal vein pressure and blood flow. The portal vein is the drainage route of the left gastric vein, so the infusion may impact stomach activity. DGE and dumping syndrome caused by digestive reconstruction may affect glycemic control, while worsened glycemic control may damage the transplanted islets via glucotoxicity. The mass of isolated islets that is infused intraportally is also critical for post-transplant glycemic control.

Since the clinical relevance of the pylorus preserving procedure has been reported for postoperative outcomes and nutritional status in pancreaticoduodenectomy,[11] this study is aimed at comparing the clinical effectiveness of non–pylorus-preserving (NPP) and pylorus-preserving (PP) procedures in patients undergoing TPIAT.

2. Patients and methods

2.1. Patient selection

The Baylor Simmons Transplant Institute patient database was queried to identify all patients who underwent a TPIAT for CP from October 2006 to March 2014. A total of 83 patients with the follow-up data at 1 year were identified. Among of them, ten patients who had previous pancreas or gastric surgery were eliminated in this study. And then total 73 patients were categorized into an NPP group (N = 16) and PP group (N = 57). All patients were evaluated and diagnosed as chronic pancreatitis by a multidisciplinary team, including a gastroenterologist, endocrinologist, and transplant surgeon. The diagnosis of CP was based on the patient's history, laboratory results, computed tomographic scans, endoscopic retrograde pancreatography, endoscopic ultrasonography, magnetic resonance imaging, and pathologic diagnosis. The indications for surgery were intractable pain despite medication, pancreatic duct stent insertion, or celiac nerve block. In this study, preoperative patient background, intraoperative conditions, postoperative complications, and nutritional status were investigated to evaluate the clinical significance of the preservation of the pylorus ring. This study was approved by and performed according to the guidelines set by the Baylor University Medical Center institutional review board.

2.2. Operative procedure and islet cell transplantation

The TP procedure was performed in all of the patients, including splenectomy and removal of the distal common bile duct, and pancreatic blood supply was preserved during surgery as long as possible to minimize islet cell ischemia. Ligation of the splenic artery and gastroduodenal artery was delayed until final step of the procedure. In this study, all of the surgical procedures were performed by single surgeon, who made decision on pylorus preservation based on the degree of inflammation and adhesion around pylorus ring. In the PP group, the pylorus ring was preserved, while in the NPP group, the subtotal stomach was preserved. Retrocolic gastrointestinal reconstruction was performed with two-layer anastomosis. After the removal of spleen and duodenum from the pancreas on the back table, the pancreatic duct was cannulated and the pancreas was placed in a container with cold preservation solution. Subsequently, it was transferred to a clinical good manufacturing practice facility for islet isolation processing.

Liberase MTF with Thermolysin MTF (Roche, Basel, Switzerland) or Collagenase NB with neutral proteases (SERVA Electrophoresis GMbH, Heidelberg, Germany) was infused into the pancreatic duct for digestion. Islets were isolated by the modified Ricordi method, which has been previously described.[12–14] When the tissue volume (mL) exceeded 0.25 times body weight (kg), islets were purified with a COBE 2991 cell processor (Caridian BCT Inc., Lakewood, CO) using a density-adjusted iodixanol-based continuous density gradient. Endotoxin testing, Gram staining, and bacterial and fungal cultures were completed on the final products and used as indicators for sterility. Isolated islets were infused into the portal vein via the superior mesenteric vein with heparin (70 U/kg body weight) while the patient was under general anesthesia. The portal vein pressure was regularly monitored during the islet infusion.

2.3. Postoperative care and assessment of clinical outcome

All patients were monitored for strict blood glucose control with continuous insulin injection for 48 h. Afterwards, the insulin injection was converted to a basal bolus insulin injection. Blood glucose levels were maintained at a normal level during the hospital stay. All patients were discharged with an individual insulin regimen. Oral intake was routinely started 7 days after the surgery unless postoperative complications such as DGE occurred. H2 blockers were administered postoperatively to all patients for 3 days or longer. The nutritional status of patients was assessed according to the Subjective Global Assessment of Nutritional Status rating.[15] The diagnosis of DGE was based on the classification of the International Study Group of Pancreatic Surgery.[16] The flow of the portal vein after transplantation was assessed by Doppler after surgical intervention at day 1 after transplantation. When portal vein flow was not detected by Doppler, it was considered a portal vein thrombosis.

Postoperative follow-up care was provided by the transplant surgeons and endocrinologists. Improvement of clinical symptoms was assessed in the postoperative period. Narcotic requirements were reported as a morphine-equivalent quantity per day (MEQ/d). The body weight, serum albumin, and hemoglobin A1c (HbA1c) and C-peptide levels were measured before surgery, on hospital discharge, and at each subsequent postoperative patient encounter. In TPIAT, the primary endpoints of metabolic outcomes were defined as insulin independence, C-peptide > 0.3 ng/mL, and HbA1c < 6.5%. Postoperative C-peptide levels were measured after fasting at 3, 6, and 12 months. Patients with detectable C-peptide values (>0.3 ng/mL) were considered C-peptide positive. Graft function was assessed until complete graft failure (first occurrence of C-peptide < 0.3 ng/mL). Additionally, serum vitamin levels were measured at 1 year after transplantation.

2.4. Statistical analysis

The Wilcoxon two-sample test was used to compare continuous variables between the PP and NPP groups. Categorical variables were compared using the two-sided Fisher's exact test. Categorical variables are expressed as counts with percentages, and continuous variables as medians with interquartile ranges or means and standard deviations, as appropriate. A P value of ≤ 0.05 was considered statistically significant. Each clinical outcome that was measured over time was analyzed using linear mixed regression models. This method allows for the analysis of longitudinal data with multiple measurements taken on each subject by examining not only differences between subjects, but also changes within subjects across time. Adjusted post hoc multiple comparisons and pairwise multiple comparisons were performed using the Dunnett adjustment. Time-to-event variables were analyzed using Kaplan-Meier curves and compared using the log-rank test. All statistical analysis was performed using SAS 9.3 (SAS Institute, Cary, NC, USA).

Please cite this article in press as: Shahbazov R, et al., Clinical effectiveness of a pylorus-preserving procedure on total pancreatectomy with islet autotransplantation, The American Journal of Surgery (2016), http://dx.doi.org/10.1016/j.amjsurg.2016.09.051