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Prior Surgery Determines Islet Yield and Insulin Requirement in Patients with Chronic Pancreatitis

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Abstract

Background—Total pancreatectomy with islet autotransplantation (TP-IAT) is safe and effective in the management of intractable pain associated with chronic pancreatitis (CP). Prevention of pancreatogenic diabetes after TP-IAT is related to islet yield from the diseased pancreas. The purpose of this study is to compare islet yield and insulin requirement in the 76 patients who underwent different surgical procedures prior to TP-IAT at the Medical University of South Carolina between the years 2009 to 2011.

Methods—Patients were grouped into four categories based on the operation they had before TP-IAT: transduodenal sphincteroplasty or no prior surgery (TDS/NPS, n=50), Whipple or Beger procedure (WB, n=14), distal pancreatectomy (DP, n=8) or lateral pancreaticojejunostomy (LPJ, n=4). Islets were harvested from pancreases of those patients at our cGMP facility. Total unpurified islets were transplanted into patients via portal vein infusion. Pancreatic fibrosis, islet yield, cell viability and insulin requirement were measured.

Results—The pancreases of TDS/NPS and WB patients were less fibrotic, and had higher islet yield compared to those who had DP or LPJ. Higher islet yield also correlated with a greater diabetes free rate and a lesser insulin requirement at the following intervals: pre-operative, post-operative and 6 months after TP-IAT.

Conclusions—Prior surgery is strongly correlated with the extent of pancreatic fibrosis, islet yield and insulin requirements in CP patients undergoing TP-IAT. The history of prior pancreatic resection and drainage procedures may be used to predict post-operative islet function and help to determine the optimal timing for TP-IAT in CP patients.

Keywords

Islet autotransplantation; chronic pancreatitis; islet yield; prior surgery; surgical diabetes

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The authors have nothing to disclose.

INTRODUCTION

Chronic pancreatitis (CP) is a long-standing inflammation of the pancreas that alters its normal structure and functions (1, 2). Approximately 15,000 Americans are diagnosed with CP each year. Current therapies for CP patients focus on pain relief medically, endoscopically and surgically (by resection of diseased parenchyma and drainage of obstructed ducts) (3). The latter includes several commonly utilized operations, including transduodenal sphincteroplasty, Whipple procedure, Beger procedure, distal pancreatectomy and lateral pancreaticojejunostomy. Transduodenal sphincteroplasty is a procedure to resolve obstruction at the ampulla/sphincter, in which an incision is made through the duodenum and the pancreatic and bile ducts are identified and sewn open widely to allow for proper drainage (4). The Whipple procedure consists of the removal of the distal segment of the stomach, first and second portions of the duodenum, the head of the pancreas, the common bile duct, and the gallbladder. The Beger procedure involves the removal of the head of the pancreas with preservation of the duodenum, stomach and bile duct. Distal pancreatectomy allows for proper drainage of the neck region of the pancreas by removal of the tail and body of the pancreas. Lateral pancreaticojejunostomy involves excising the entire pancreatic duct lengthwise and suturing it into the intestine to allow direct drainage into the intestine (5).

Controlling pain in CP patients with medications and the above-mentioned surgeries is successful approximately 80% of the time over the short-term (3, 6-8). In patients with intractable pain and those with diffuse small duct diseases, total pancreatectomy with islet autotransplantation (TP-IAT) can be an ideal treatment option.

Compared to other treatment options for CP, TP-IAT has a higher potential to eliminate pancreatic pain without total sacrifice of the endocrine function of the pancreas. This procedure is currently performed in several centers across the United States, Australia, and in Europe. Data from other studies and our own show that TP in combination with IAT is a safe and effective option for patients with end stage CP (9-15). Improved quality of life and decreased requirement for narcotic analgesics were shown after TP-IAT. A significant percentage of patients are diabetes-free with some being insulin-independent for the rest of their lives (16, 17). All patients that do require insulin have hypoglycemic awareness and are shown to have improved metabolic control and quality of life. Nonetheless, since the etiology of pancreatic pain is extremely complex and poorly understood, TP-IAT is not currently being considered first line of treatment for most CP patients. However, since resection and drainage procedures can damage pancreatic islets, and affect harvest (due to lower achievable intraductal pressures) and yield (due to lower available parenchyma), further data are needed to help identify the patient population who can benefit the most from each procedure, explore and better understand the potential downsides of advising a conservative resection or drainage procedure prior to a TP-IAT, vs. TP-IAT alone in selected patients to achieve optimal outcome.

We undertook this study to investigate how different types of surgeries performed before TP-IAT determines final islet yield and insulin requirement in patients after TP-IAT. Such

information is crucial for physicians and patients to choose the optimal therapy for patients with chronic pancreatitis.

RESULTS

Prior Surgery vs. Pancreas Quality

To evaluate the effect of prior surgeries on the extent of tissue fibrosis, each pancreas was examined in the pathology laboratory using a semi-quantitative score system. As shown in Table 1, in TDS/NPS patients, 41.67% of the pancreases were soft, 41.67% were moderate and the other 16.67% were hard (n=48, data from two patients were missing). The majority of pancreases (64.4%, n=14) from patients who had WB procedures were moderate in fibrosis and had the least number of severely fibrotic tissues (7.14%) compared to those from other groups. In contrast, the majority of the pancreases (87.5%, n=8) derived from patients who had distal pancreatectomy were severely fibrotic with one being moderate in fibrosis. Pancreases from patients who had LPJ tended to be harder as well (50% of them were moderate, 25% were hard, n=4), which correlated with the significantly longer disease duration in this group of patients (Supplemental Digital Content, Table 1).

Type of Surgery vs. Islet Yield

Total islet yield from each patient was assessed in aliquots from final islet preparation. On average, the islet equivalent number (IEQ) obtained from the different patient population was $364,344 \pm 268,504$ (range: 4,288 to 1,168,725) for TDS/NPS, $206,975 \pm 213,640$ (range: 14,312 to 816,425) for WB, $113,689 \pm 191,492$ (range: 969 to 534,015) for DP; and $37,418 \pm 26,835$ (range: 3,667 to 64,562) for LPJ. There is a significant difference of islet yield among different groups as analyzed by the ANOVA test ($p < 0.001$). The IEQ/kg body weight transplanted were also significantly different among different groups ($p < 0.05$), with $4,980 \pm 3,791$ (range: 49 to 16,010) for patients in the TDS/NPS group, $3,163 \pm 3,962$ (range: 235 to 15,404) for patients in the WB group, $1,011 \pm 1,421$ (range: 14 to 3,317) and 579 ± 408 (range: 61 to 1,058) for patients who had DP or LPJ, respectively (Fig.1A). The differences among the groups on IEQ/kg appeared driven by the difference between TDS/NPS/WB and DP/LPJ. We also measured the final pellet weight after islet harvest. The value was 16.44 ± 11.39 grams for TDS/NPS and 3.84 ± 4.54 grams for LPJ patients, which was significantly different ($p = 0.002$). However, the pellet weights in patients who had WB and DP were very similar, at 7.41 ± 5.57 and 6.20 ± 9.53 grams, respectively (Fig.1B), even though the islet yield was significantly higher in those who had WB.

Prior Surgery vs. Elapsed Time from Tissue Excision to Islet Transplant

The average time elapsed from pancreas excision to islet re-infusion into the patient was 314.24 ± 52.44 minutes for TDS/NPS patients; 289.00 ± 32.40 minutes for WB patients; 292.38 ± 84.55 minutes for DP patients and 280.50 ± 24.57 minutes for LPJ patients (Fig. 2). Thus, it seems that longer time is needed to process the pancreas from TDS/NPS patients than pancreases from the other groups. If anything, this potential confounding would have lowered yield in TDS/NPS patients compared with patients with prior resections.

Type of Surgery vs. Insulin Requirement Pre- and Post-operation

To evaluate the function of transplanted islets, daily insulin requirements were measured before surgery, at discharge after TP-IAT, and 6 months after surgery. As shown in Fig 3A, most patients who had TDS/NPS and WB procedures were diabetes-free before TP-IAT, compared to only 50% of the patients that were diabetes free in the DP and LPJ groups. At 6 months after surgery, the diabetes-free rate was 46% in the TDS/NPS group (n=50), 43% in the WB group (n=14) and 25% in the DP group (n=8, Fig.3B). In addition, 20% of the TDS/NPS group, 14% of the WB group and 25% of the LPJ group required less than 10 u/day of daily insulin at 6 months after surgery. All four patients from the LPJ group required insulin treatment.

Among the patients requiring insulin on a daily basis, the average insulin requirements at 6 months ranged from 22 U/day to 35 U/day, which was not significantly different between the groups (Fig. 4A). Most TDS/NPS and WB patients have detectable c-peptide value 6 months after surgery (Fig.4B) and had a relatively lower HbA1c level (Fig. 4C). In contrast, patients in the DP group had the highest HbA1c level and the lowest proportion of patients with detectable c-peptide compared to those who had TDS/NPS and WB pre-operatively.

DISCUSSION

TP-IAT is currently undertaken to attempt to eliminate pancreatic pain, while avoiding surgically-induced diabetes, in selected patients with end-stage chronic pancreatitis. Long-term pain relief and glycemic control has been achieved in a high percentage of patients (18-20). However, this procedure is currently not the first-line surgical therapy for CP patients partly due to operative morbidity and lack of data to predict outcomes, especially in patients with earlier disease (21-23). Thus, indicators that can predict the outcomes of TP-IAT are urgently needed for the advancement of this field. Studies have shown that the degree of histopathologic changes and stimulated c-peptide level before surgery determine islet yield (24-26). Our study showed strong evidence that prior pancreatic surgery before TP-IAT can affect islet yield and insulin requirement after TP-IAT. Although it has been observed that patients who have had distal pancreatectomy or LPJ procedures have lower islet yield and a lower rate of insulin independence (27), this is the first detailed report that compares side by side how different commonly used surgeries predict islet yield and graft function after TP-IAT.

In our patient population, we observed a strong correlation between types of prior surgeries and total islet yield per pancreas. Firstly, surgeries involving resection of pancreatic parenchyma, not surprisingly, negatively affected islet yield; i.e., pancreas from patients in TDS/NPS group had the highest islet yield compared to other groups. TDS and NPS patients were grouped together here since there was no major resection of pancreatic parenchymal involved in those patients. Sphincteroplasty has been shown to lead to colonization of the duct by bacteria from the colon, and therefore may play a role in fibrosis (28), which was not observed in our study. Secondly, it appears that resection of different regions of the pancreas determine islet yield as well. Although the head of the pancreas are generally more fibrotic than the resection area in CP patients (29), islet yield from the WB group was still significantly greater than in the DP group. This appears to be explained by the fact that there

are more islets residing in the pancreas tail compared to the pancreatic head, so resection of the pancreatic tail (DP) leads to more islet loss compared to the resection of the head and body of the pancreas (WB).

Islet yield in patients who had LPJ (Puestow) procedure before TP-IAT had the lowest islet yield compared to other procedures, even though only drainage procedures (without resection) had been performed in these patients, this is keeping with findings from other groups (30). The lower yield in LPJ has several potential explanations. It may be explained by the fact that patients who have a LPJ procedure usually have dilated duct disease, with atrophy, and a greater extent of parenchymal destruction (31). That is, the pancreases in the LPJ group have greater exocrine and endocrine tissue destruction than those with minimal duct disease or non-dilated chronic pancreatitis. Moreover, in addition to possible parenchymal destruction, drainage procedures themselves may increase scarring in the pancreas, comprise ability to perform intraductal perfusion of collagenase due to the increased ductal pressures and reduce islet yield. Lastly, LPJ patients had the longest duration of disease (e.g., 17.6 ± 16.5 for LPJ vs. 6.1 ± 4.4 for TDS/NPS, Supplemental Digital Content, Table 1), which may significantly impact the islet yield due to long-term inflammation in the diseased pancreas.

Our study reveals that the extent of tissue fibrosis determines islet yield as well. The more fibrotic the pancreas, the fewer number of islets can be obtained. This may be due to diminished islets in the fibrotic pancreas due to the disease process, or that fibrotic pancreases are more difficult to process and harder to digest by enzyme and mechanical activity. There was no difference in islet cell viability observed from the islets isolated from pancreases from different groups. Islet cells have an average viability of >95% after isolation and before transplantation (data not shown).

Our study also indicates that there is a strong correlation between islet yield and islet function after transplantation. The larger the number of islets transplanted, the greater the likelihood that the patient will be diabetes free after surgery. For example, patients who had TDS/NPS or WB procedures had more islet yields and thus a greater chance to be diabetes free compared to patients whose islet-rich region was removed by a DP or altered by a LPJ procedure before TP-IAT. In contrast, the LPJ and DP surgery groups showed significant reduction of islet yield and thus a lesser chance of insulin independence after surgery. Notably, patients who underwent DP prior to TP-IAT had the highest HbA1c levels and fewer patients with detectable c-peptide compared to patients from other groups (Fig. 4). Patients undergoing WB procedure received fewer IEQ than patients with TDS/NPS; however, their outcomes are the same or better in terms of insulin requirement, c-peptide, and HbA1c. Thus, it seems that in general patients who received >2500 IEQ/kg islets have a better chance to be diabetes free compared to those who received less than 1000 IEQ/kg islets, which has been observed by other groups as well (23, 32).

This data can help physicians identify the most suitable patient population who will benefit the most from TP-IAT and optimize patient selection. Strong evidence on the definitive treatment of chronic pancreatitis is elusive (33). It is commonly agreed that the ultimate goal for the treatment of chronic pancreatitis is to relieve the intractable pain caused by the

disease and to prevent exocrine and endocrine insufficiency (23). Generally patients with small duct (<7mm) disease that have failed drainage procedures are first recommended for resectional procedures including the Whipple procedure, Beger procedure, distal pancreatectomy or total pancreatectomy. These procedures improve pain symptoms in >50% of patients at 5 years following surgery (34-36). Patients with dilated pancreatic duct (>7mm) are normally recommended for LPJ. A consensus statement by the American Gastroenterological Association shows that 80% of patients with LPJ had short-term improvement of pain and 60-70% achieved continued pain relief 2 years post surgery, with only 0-5% morbidity and mortality, subjective improvement of lifestyle, decreased narcotic use similar to the pain relief outcome as islet autotransplantation (37-41). Since LPJ has satisfactory outcomes assessed by improvement in pain and a lower morbidity than resection procedures, it still has a role in the management of chronic pancreatitis today. However, as evidence is obtained from the TP-IAT experience, the role of LPJ may change.

Based on data from other labs and our own, pancreatic surgeries are associated with significant islet cell loss, and a greater likelihood of reduced islet yield and postoperative diabetes. Although our patient number is very limited here, patients who had DP and LPJ pre-operatively tend to have lesser islet yield and thus are more likely to develop postoperative diabetes. Therefore, we suggest to perform TP-IAT as early as possible in the patient population that are not likely to respond well to previous procedures in order to maximally preserve islet mass, to avoid a prolonged period of ineffective treatments, and to minimize the staged approach to patient care represented by reoperative therapy (42).

Nevertheless, our data confirms that even patients with prior surgeries including LPJ do well after TP-IAT as determined by quality of life and diabetes control. For example, although all four patients who had LPJ previously need insulin treatment, one patient only requires an average of 9 units of insulin per day and another patient that requires 13 units of insulin per day at 6 months after transplantation, both with much improved quality of life (data not shown).

In conclusion, TP-IAT is an efficient procedure for pain relief in patients with end-stage chronic pancreatitis. Prior surgery, including surgeries other than LPJ, is strongly correlated with islet yield and post-operative insulin requirements in CP patients who had TP-IAT. Islet yield can be compromised by prior surgery due to the fibrotic nature of the respective pancreas, the respective region involved in the resection of the pancreas, and the resulting ductal anatomy. Our data can help to improve patient selection and patient expectations when TP-IAT is considered in patients with intractable pain due to CP, and help make decisions regarding the downsides of trying other surgical options before considering TP-IAT.

MATERIALS AND METHODS

Patient Population

Data from 76 chronic pancreatitis patients who have undertaken extensive pancreatectomy with islet autotransplantation at the Medical University of South Carolina between March 2009 and December 2011 were reviewed (3). The mean patient age was 42.1 years (standard

deviation, SD 11.4), the mean duration of symptoms was 7.5 years (SD 6.4), and the initial mean body mass index (BMI) was 27.2 (SD 6.2). The mean follow-up was 18 months, with a range of 6-24 months (Supplemental Digital Content, Table 1). Regarding insulin-/diabetes-free rates, only 6-month data were analyzed as the data were insufficient at 24 months.

Patients were divided into four groups based on their previous operations before undergoing TP-IAT. The four groups include: transduodenal sphincteroplasty or no prior surgery (TDS/NPS, n=50), Whipple or Beger procedure (WB, n=14), distal pancreatectomy (DP, n=8) and lateral pancreaticojejunostomy (LPJ, also called a Puestow procedure, n=4). Patients that underwent no parenchymal resection but transduodenal sphincteroplasty and patients that had no prior surgery before TP-IAT were grouped together. The Whipple and Beger procedures were also grouped together since both involve the removal of the head of the pancreas. This study was approved by the Institutional Review Board at the Medical University of South Carolina and patient consents were obtained.

Pancreas Evaluation

Each pancreas was weighed and examined for fibrosis by palpation and the extent of fibrosis was confirmed in the pathology lab by a histologic fibrosis semiquantitative score system that is based on a 0-3 score of interlobular and intralobular fibrosis by microscopy as described (43). Based on the severity of fibrosis, the pancreases were classified into 3 categories: soft (no obvious fibrotic tissue), moderate (less than 50% of pancreas with fibrotic tissue), and hard (greater than 50% of pancreas with fibrotic tissue).

Islet Harvest and Transplantation

Each patient's pancreas was transferred from the clinic center to the current good manufacturing practice (cGMP) facility at the Medical University of South Carolina in compliance with federal regulations. Islets were harvested from the pancreas using the modified Ricordi method (44). Liberase MTF (Roche, Indianapolis, IN) was infused into the main pancreatic duct or injected directly into the pancreas for distension. Islets were released from other tissues by enzyme digestion and mechanical forces. Islet yield was assessed by the dithizone (Sigma Aldrich, St. Louis, MO) staining and converted to a standard number of islet equivalents (IEQ) of islets with diameter standardizing to 150µm. Islet cell viability was assessed by SytoGreen 13 (25µM, Invitrogen, Carlsbad, CA) and ethidium bromide (50µM, Sigma) fluorescent staining based on membrane integrity. Total unpurified islets were re-suspended in 5% human albumin with heparin (70U/kg body weight) for infusion. Endotoxin, gram staining, bacterial and fungal cultures were measured in the final products and used as indicators for sterilization. Islets were infused into the portal vein via the mesenteric vein of the patient who was under general anesthesia. Time elapsed from pancreas excision to islet re-infusion into patient was recorded, which included the time needed for tissue transportation and islet preparation.

Measurement of Clinical Outcomes

Average daily oral narcotic requirement standardized as morphine equivalents (MEs), average daily insulin requirement, HbA1c and c-peptide levels were recorded before

surgery, on hospital discharge, and at each subsequent postoperative patient encounter as previously described (3). Pre-operative c-peptide levels were measure after fasting and c-peptide at 6 months was measured without fasting. Patients with detectable c-peptide value (>0 ng/ml) were considered c-peptide positive. Study data were managed using REDCap electronic data capture tools hosted at the Medical University of South Carolina.

Statistical Analysis

Data were analyzed by the ANOVA analysis for continuous variables, and Fisher exact of proportions. Differences between groups were compared. A p value of <0.05 was considered statistically significant. Values are shown as mean $\pm$ standard deviation. Sample size was considered too low to attempt multivariate modeling, but potential confounding and effect modification was explored with selected subgroup univariate analyses.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CP	chronic pancreatitis
DP	distal pancreatectomy
LPJ	lateral pancreaticojejunostomy

TDS/NPS	transduodenal sphincteroplasty or no prior surgery
TP-IAT	total pancreatectomy with islet autotransplantation
WB	Whipple or Beger procedure

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Fig.1. Type of surgery vs. final pellet weight and IEQ/kg transplanted

A. Average of islet IEQs transplanted per kilogram body weight in patients who had transduodenal sphincteroplasty or no prior surgery (TDS/NPS, light grey bars), Whipple/Beger Procedure (WB, dark grey bars), distal pancreatectomy (DP, black bars) and lateral pancreaticojejunostomy (LPJ, lined bars). **B.** Final average islet pellet weight (gram) after islet isolation and before transplantation was measured in the different patient groups. There is a significant difference of islet yield among different groups as analyzed by the ANOVA test ($p < 0.001$).

Fig.2. Elapsed time (minutes) from tissue excision to islet transplant

Longer time is needed to process pancreases from patient who had TDS/NPS (light grey bar), compared to patients who had WB (dark grey bar), DP (black bar) or LPJ (lined bar) procedures before TP-IAT.

Fig.3. Percentage of diabetes-free patients in each group before surgery (A) and at 6 months after surgery (B)

Data represent percentages of patients who do not need insulin to control their blood glucose levels. TDS/NPS (n=50, light grey bars), WB (n=14, dark grey bars), DP (n=8, black bars) and LPJ (n=4, lined bars).

Fig. 4. Diabetes management at 6 months post-operative

A. Average daily insulin requirement in patients that need insulin injection. **B.** Percentage of patients who were C-peptide positive at 6 months after surgery. **C.** Patients' HbA1c levels after TP-IAT. TDS/NPS (light grey bars), WB (dark grey bars), DP (black bars) and LPJ (lined bars, n=2). C-peptide level in LPJ group only include 2 patients, the other 2 values were missing at 6 months). All other measurements include all patients in each group.

Table 1

Extent of pancreas fibrosis measured before islet isolation.

Type of Surgery Prior TP-IAT	Soft % (n)	Moderate % (n)	Rock hard % (n)
TDS/NPS	41.67 (20)	41.67 (20)	16.67 (8)
WB	28.57 (4)	64.4 (9)	7.14 (1)
DP	0 (0)	12.5 (1)	87.5 (7)
LPJ	25 (1)	50 (2)	25 (1)