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Short- and long-term surgical outcomes of total pancreatectomy with islet autotransplantation: A comparative analysis of surgical technique and intraoperative heparin dosing to optimize outcomes

Robert Naples*, R. Matthew Walsh, Jonah D. Thomas, Breanna Perlmutter, John McMichael, Toms Augustin, Robert Simon**

Department of General Surgery, Digestive Disease and Surgery Institute, Cleveland Clinic, Cleveland, OH, USA

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ABSTRACT

Background: Total pancreatectomy with islet autotransplantation (TP-IAT) is an uncommon surgical procedure with unique perioperative management. We evaluated the short- and long-term morbidity and mortality of TP-IAT to optimize surgical technique and heparin dosing during islet autotransplantation.

Methods: Eighty patients with chronic pancreatitis undergoing TP-IAT were reviewed. Primary outcome was to evaluate morbidity and mortality based on operative technique: classic (resection of antrum) vs pylorus-preserving. Secondary outcome was to evaluate the effect of heparin dosing (<60 vs ≥ 60 units/kg) during islet autotransplantation on postoperative hemorrhage and portal vein thrombosis (PVT) rates.

Results: There was no 90-day mortality, and median length of stay was 9 days. All patients underwent an open operation with 53 (66%) pylorus-preserving resections. The 30-day morbidity rate was 39%, with no difference between operative technique ($p = 0.82$). The median dose was different for each heparin group (<60: 52 units/kg vs ≥ 60: 66 units/kg, $p < 0.0001$). No difference was observed in postoperative hemorrhage rates between heparin groups (<60: 9% vs ≥ 60: 9%, $p = 0.97$), with no known incidence of PVT. Median follow-up was 36 months (IQR, 14–71). Morbidity >30 days after TP-IAT was 43% with a higher rate in the pylorus-preserving group (55% vs 15%, $p < 0.0001$), mainly attributed to marginal ulcer formation (15% vs 0%, $p = 0.03$).

Conclusions: A classic TP-IAT technique should be universally adopted to achieve optimal outcomes, particularly to prevent the formation of marginal ulcers. When considering PVT versus postoperative hemorrhage risk, a lower heparin dose nearing 50 units/kg is optimal. These findings highlight potential areas for future improvement.

Introduction

Chronic pancreatitis (CP) is a debilitating disease characterized by pancreatic inflammation and fibrosis causing pain as well as endocrine and exocrine pancreatic insufficiency [1,2]. While multiple factors are implicated in the development of CP, including genetics and environmental, alcohol accounts for the majority of cases [3]. Medical and endoscopic therapies are typically first-line treatment options with surgery reserved for those patients with refractory pain, suspicion for cancer, or local complications related to pancreatitis such as biliary or duodenal obstruction [4–6].

Surgical options include pancreatic ductal drainage, partial or total parenchymal resection, or a combination of these two procedures. The optimal operative approach is guided by extent of pancreatic involvement, pancreatic mass and concern for cancer, ductal diameter, and associated adjacent structure pathology (eg, bile duct or duodenal stenosis) [6,7]. Peripancreatic sensory nerve damage is one possible mechanism for intractable pain in CP and provides a rationale for total pancreatectomy [8,9]. However, metabolic consequences of the apancreatic state, with the most significant being development of brittle diabetes, limit the role of

* Corresponding author.
** Corresponding author.
E-mail addresses: naplesr2@ccf.org (R. Naples), simonr@ccf.org (R. Simon).

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total pancreatectomy alone for CP [10]. Therefore, in an effort to preserve pancreatic endocrine function, total pancreatectomy with islet autotransplantation (TP-IAT) has been developed. This results in approximately one-third of patients achieving insulin independence at one year while another one-third gain partial islet cell function, and the majority of patients (~80%) are able to have adequate blood sugar control as evidenced by a HgbA1c < 7 [11–13]. Moreover, TP-IAT can alleviate pain and improve quality of life in those patients with refractory CP [13–17].

Given the technical complexity associated with the operation, morbidity and mortality rates continue to be significant [17,18]. Thus, there remains opportunity for improvements in surgical technique and islet infusion protocols to mitigate postoperative complication risks following TP-IAT. While many endpoints like islet function and pain relief have already been examined, this study is directed at evaluating and improving surgical outcomes. The effect of a classic (resection of the antrum) or pylorus-preserving technique along with heparin dosing during islet autotransplantation on postoperative surgical outcomes are unclear. This study evaluated the short- and long-term morbidity and mortality following TP-IAT at our institution to optimize the surgical technique and intraoperative heparin dosing during islet autotransplantation.

Methods

Following Institutional Review Board approval, a retrospective review of all patients with CP undergoing TP-IAT at the Cleveland Clinic from 2007 to 2019 was conducted. Patients with a prior partial pancreatic resection or drainage procedure were included. Selection criteria for TP-IAT at our institution has been previously published [17]. Briefly, patients with CP related to a genetic etiology or refractory to medical and/or endoscopic therapies with no pancreatic ductal dilatation are considered for a TP-IAT. Each patient is evaluated by a multidisciplinary team including hepatopancreatobiliary surgeons, gastroenterologists, endocrinologists, nutrition therapists, social workers, psychologists, and pain specialists. A mixed-meal test is included in the workup to evaluate islet function and determine the potential success of an islet autotransplantation. In an effort to differentiate between centralized and visceral pain, a differential pain block is performed. Subsequently, consensus is reached that the patient would benefit from surgical removal of the pancreas. Finally, patients are required to be abstinent from alcohol and smoking for at least 6 months prior to the procedure.

Data collection

The electronic medical record (EMR) was manually reviewed for patient demographics, co-morbidities, prior pancreatic surgeries, operative details, and postoperative complications. Postoperative complications were categorized into two groups based on timing from TP-IAT: early (≤30 days) and late (>30 days). Additionally, early postoperative complications were classified by the Clavien-Dindo grading system [19]. Delayed gastric emptying (DGE) was graded according to the International Study Group of Pancreatic Surgery consensus [20]. The need for prokinetic agents was not included in our definition of DGE because all patients routinely receive metoclopramide for 2 weeks postoperatively. DGE was defined by the need for nasogastric drainage after postoperative day 3, an inability to tolerate oral intake by postoperative day 7, or the need for supplemental enteral nutrition via a feeding tube after the first postoperative week, without evidence of mechanical gastric obstruction [20]. All patients have a nasojejunal tube placed intraoperatively for immediate postoperative enteral feeds until they are taking adequate oral food intake. Gastroparesis was defined by an abnormal gastric emptying test at least 30 days after TP-IAT. Small bowel obstruction (SBO) was diagnosed based on symptoms and imaging evidence for a mechanical obstruction. Following hospital discharge from the index surgery, SBO was captured if the patient had a readmission or operative intervention related to the diagnosis. Abdominal infections were classified as organ space (OSI) or superficial site (SSI) infection. An OSI was diagnosed by axial imaging and confirmed with positive microbial cultures, whereas an SSI was diagnosed by clinical signs, such as induration, cellulitis, and leukocytosis, and/or positive microbial cultures. Patients with a marginal ulcer had an endoscopy confirming the diagnosis.

The amount of heparin in units/kg administered during islet autotransplantation was recorded and categorized into two groups: <60 and ≥ 60 units per kilogram (units/kg). Portal pressures during islet autotransplantation were recorded. Baseline measurements were obtained prior to islet infusion and after the completion of each infused islet bag. The change in portal pressure (ΔPP) was defined as the difference between the maximum pressure measured during islet infusion and the baseline measurement. The total amount of islet cell equivalents (IEQ) infused per kilogram (kg) of body weight were retrieved. Postoperative hemorrhage was defined by 3 parameters established by the International Study Group of Pancreatic Surgery: time of onset (≤24 h vs > 24 h following completion of the operation), location (intraluminal vs extraluminal), and severity (mild vs severe) [21].

As a quaternary center with patient referrals both domestic and international, follow up for patients was variable depending on their place of residence. However, our institutional protocol requires that all patients are evaluated in the clinic 2–4 weeks following their operation then every 6 months. Moreover, patients are typically referred back to our practice for any complication related to TP-IAT, allowing us to capture the majority of events from our EMR. The date of last follow up was recorded as the last visit noted in our EMR from any provider.

Surgical technique and islet infusion

Either a pylorus-preserving or classic technique, which included resection of the antrum, was performed based on surgeon preference. To prolong the perfusion to the body and tail of the pancreas, a splenectomy is typically performed. The coronary vein is preserved to maintain venous outflow from the stomach, and the gastroduodenal artery (GDA) is ligated immediately prior to final dissection of the uncinate process and specimen removal to maintain perfusion to the pancreas and decrease warm ischemia time. Once resection is complete, the pancreas is flushed via the splenic artery and GDA with UW solution, packed on ice, and transported off-site for islet cell isolation and preparation. There is approximately an 8–10 h total time lapse between complete removal of the specimen and islet infusion. The gastrointestinal and biliary reconstruction is completed, fascia and skin closed, and the patient remains intubated with transfer to the post-anesthesia care unit (PACU). For both techniques, the reconstruction is performed in the same manner. The jejunum is brought behind the mesenteric vessels to lie in the position of the native duodenum and advanced to create the hepaticojejunostomy. Either an antecolic double layer hand-sewn gastrojejunostomy (classic) or single layer hand-sewn duodenojejunostomy (pylorus-preserving) is performed 45 cm distal to the hepaticojejunostomy. The patient is cared for in PACU until islet autotransplantation is to be performed.

When the islet processing is complete, our surgeons are notified and preparations for the islet autotransplantation is undertaken. The patient is brought back to the operating room, and the prior

laparotomy is opened. An exploratory laparotomy is performed to confirm hemostasis and examine the biliary and gastrointestinal reconstruction. The splenic vein remnant is typically the route for islet infusion which has already been prepared. A 10-gauge angiocath is placed into the end of the vein and doubly secured, and portal pressure obtained with a manometer. Just prior to infusion, the islet cells are mixed with heparin. Heparin dosing is weight based, with the amount administered based on surgeon preference. Once infusion is complete, the splenic vein is ligated, and hemostasis is obtained. The abdomen is closed, and the patient is transferred to the intensive care unit (ICU) for postoperative care. Due to the heparin administration with the islet autotransplantation, patients have an activated partial thromboplastin time (aPTT) laboratory test completed upon admission to the ICU.

Postoperative care

Patients are started on an insulin drip in the PACU, and endocrinology is consulted for management of blood glucose levels. Typically, extubation occurs the morning after surgery and the patient is transferred out of the ICU within 24 h. Enteral feeds are started on the first postoperative day via an intraoperatively placed nasojejunal feeding tube. Enteral feeds are continued until the patient tolerates solid oral intake for at least 24 h. If they develop delayed gastric emptying, then they are discharged with the nasojejunal feeding tube and home tube feeds. All patients take Creon to prevent pancreatic exocrine insufficiency. Proton pump inhibitors are prescribed upon discharge for 3 months to prevent marginal ulceration and metoclopramide for 2 weeks to promote gastric motility.

Study outcomes

The primary outcome was to compare postoperative morbidity and mortality rates based on operative technique: classic versus pylorus-preserving. Morbidity comprised both early and late postoperative complications, with each being considered as a separate group. Subgroup analysis was also performed based on Clavien-Dindo grade.

The secondary outcome was to evaluate postoperative hemorrhage and portal vein thrombosis (PVT) rates based on the dose of heparin (units/kg) administered during islet autotransplantation. Comparisons were performed on the two heparin dosing groups: <60 and ≥ 60 units/kg. Maximum portal pressure measured during islet infusion, ΔPP, and islet cell yield were analyzed and compared based on incidence of postoperative hemorrhage and intraoperative heparin administration. Additional analysis was performed on the aPTT test results to determine if there was a difference based on heparin administration dose. Routine postoperative imaging was not performed to evaluate for PVT. Patients were only captured if imaging, such as a liver vascular ultrasound or computed tomography scan, was done for clinical symptoms or suspicion; long-term imaging was reviewed when available.

Statistical analysis

Categorical variables are reported as total frequencies with percentages, and comparisons were made using a Pearson's chi-square test. Continuous variables are reported as median with interquartile ranges (IQR). Comparisons were made with a paired *t*-test. A $p < 0.05$ was considered statistically significant. Analyses were performed using JMP (version 14.0, Cary, NC).

Results

Study population

Eighty patients underwent TP-IAT with a median follow-up of 36 months (IQR, 14–71). The pylorus-preserving technique had a longer follow up when compared to the classic (54 [IQR, 20–85] vs 20 [IQR, 11–35] months, $p < 0.0001$). Median age was 39 years (IQR, 31–50) and 58% of patients were female. Overall, fourteen (18%) patients had prior pancreatic surgery. Five patients had a prior drainage procedure (4 lateral pancreaticojejunostomy and 1 surgical cystogastrostomy), six patients had a prior pancreatic resection (4 distal pancreatectomy, 1 pancreatoduodenectomy, and 1 central pancreatectomy followed by a distal pancreatectomy), and three patients had a combined pancreatic drainage and resection (2 Frey and 1 Beger). CP was idiopathic in 51% of the cases, and hereditary and alcohol related in 20% and 14%, respectively. Median duration of disease was 7 years (IQR, 3–11) prior to TP-IAT.

In the cohort, 53 patients (66%) underwent a pylorus-preserving technique, primarily earlier in our experience, and 27 patients (34%) a classic technique. A concomitant splenectomy was performed in 57 patients (71%). There was no difference in demographics, co-morbidities, or clinical characteristics based on surgical technique (Table 1).

Operative details and morbidity

Table 2 shows the operative details and 30-day morbidity of TP-IAT by surgical technique. Overall, median operative time was 363 min (IQR, 314–404) and estimated blood loss (EBL) was 400 mL (mL) (IQR, 200–600). No difference was observed in operative time ($p = 0.36$) or EBL ($p = 0.14$) when stratified by surgical technique.

The 30-day morbidity was 43% with a 9 day (IQR, 7–14) median hospital length of stay (LOS). The most common 30-day postoperative complication was postoperative hemorrhage ($n = 7$, 9%). Clavien-Dindo grade I, II, IIIa, IIIb, IVa, IVb, and V complications was observed in 11%, 33%, 16%, 10%, 4%, 0%, and 0%, respectively. Five patients (6%) developed an OSI, while one patient (1%) had an SSI. Other infectious complications were pneumonia ($n = 4$, 5%), *Clostridium difficile* colitis ($n = 4$, 5%), and urinary tract infection ($n = 1$, 1%). Two patients (3%) with DGE were a grade C, while one patient (1%) was a grade B. One patient with a grade C DGE needed a decompressive gastrostomy tube for management, and the patient with a grade B DGE had resolution of symptoms with a pyloric Botox injection. One patient (1%) developed an ileus and underwent endoscopic colonic decompression for management, and another patient (1%) who had a gastrojejunostomy tube placed at the TP-IAT operation had a leak at the gastrostomy site. One (1%) patient had a bile leak that was treated with a percutaneous drain.

The overall 30-day morbidity was similar between the pylorus-preserving and classic technique (42% vs 44%, $p = 0.80$), and no difference was observed in the overall postoperative complications (Table 2, $p = 0.24$). Clavien-Dindo grade ($p = 0.20$) and median hospital LOS ($p = 0.49$) were similar between surgical techniques.

The overall postoperative morbidity >30 days after TP-IAT was 43%. The most common complications were SBO ($n = 8$, 10%) and marginal ulcer ($n = 8$, 10%). All SBO events were related to adhesive disease, with no known incidences of internal hernias. There was no overall difference in the late complications between surgical approach ($p = 0.22$). Yet, when evaluating the total number of complications, the pylorus-preserving technique had a higher rate compared with the classic technique (55% vs 15%, $p < 0.001$). Moreover, the marginal ulcer rate was higher in the pylorus-preserving approach compared with classic technique (15% vs 0%, $p = 0.03$). Six patients (8%) developed an incisional hernia, with

Table 1
Demographics and clinical characteristics.

	Pylorus-preserving (n = 53)	Classic (n = 27)	p
Gender			
Female	29 (55%)	17 (63%)	0.48
Age (yrs); median [IQR]	36 [25, 50]	42 [35, 52]	0.15
BMI; median [IQR]	23.3 [21.0, 30.0]	23.0 [19.1, 27.3]	0.17
Co-morbidities			0.20
HTN	9 (17%)	8 (30%)	
COPD	4 (8%)	0 (0%)	
CKD	0 (0%)	1 (4%)	
CAD	2 (4%)	1 (4%)	
HLD	10 (19%)	3 (11%)	
Former history of smoking	30 (57%)	18 (67%)	0.39
Former history of alcohol	18 (34%)	10 (37%)	0.79
Prior pancreatic surgery	7 (13%)	7 (26%)	0.24
Duration of disease (yrs); median [IQR]	6 [3, 11]	7 [4, 10]	0.74
Etiology of CP			0.68
Idiopathic	25 (47%)	16 (59%)	
Alcohol	7 (13%)	4 (15%)	
Hereditary	13 (25%)	3 (11%)	
Pancreatic divisum	5 (9%)	2 (7%)	
Other[a]	3 (6%)	2 (7%)	

[a] Hypertriglyceridemia, medication-induced, and sphincter of Oddi dysfunction.

Table 2
Operative details and morbidity by surgical technique.

	Pylorus-preserving (n = 53)	Classic (n = 27)	p
Operative time (mins); median [IQR]	367 [336, 405]	352 [295, 396]	0.36
EBL (mL); median [IQR]	400 [250, 750]	300 [150, 500]	0.14
Hospital LOS (days); median [IQR]	10 [7, 15]	9 [7, 11]	0.49
30-day complications			0.24
Postoperative hemorrhage	7 (13%)	0 (0%)	
OSI	2 (4%)	3 (11%)	
SSI	0 (0%)	1 (4%)	
Other infectious complications[a]	5 (9%)	4 (15%)	
DGE	2 (4%)	1 (4%)	
SBO	1 (2%)	1 (4%)	
PE	2 (4%)	0 (0%)	
Fascial dehiscence	1 (2%)	0 (0%)	
SMV thrombosis	1 (2%)	0 (0%)	
Ileus	1 (2%)	0 (0%)	
Gastrostomy leak	0 (0%)	1 (4%)	
Bile leak	0 (0%)	1 (4%)	
Total	22 (42%)	12 (44%)	0.80
Clavien-Dindo Grade			0.23
I	3 (6%)	6 (22%)	
II	18 (34%)	9 (33%)	
IIIa	8 (15%)	5 (19%)	
IIIb	7 (13%)	1 (4%)	
IVa	2 (4%)	1 (4%)	
IVb	0 (0%)	0 (0%)	
V (mortality)	0 (0%)	0 (0%)	
>30-day complications			0.22
SBO	6 (11%)	2 (7%)	
Marginal ulcer	8 (15%)	0 (0%)	**0.03**
Incisional hernia	6 (11%)	0 (0%)	
OSI	2 (4%)	2 (7%)	
DGE	1 (2%)	0 (0%)	
Gastroparesis	3 (6%)	0 (0%)	
Cholangitis	2 (4%)	0 (0%)	
Gastric outlet obstruction	1 (2%)	0 (0%)	
Total	29 (55%)	4 (15%)	**<0.001**

[a] Pneumonia, Clostridium difficile colitis, and urinary tract infection.

none being associated with an SSI or OSI. Two patients (3%) developed cholangitis, with one related to a hepaticojejunostomy stricture and another to a small intrahepatic duct stricture. One patient (2%) with DGE was associated with the pylorus-preserving technique and was a grade C, resolving with prokinetics. Three patients (4%) with a pylorus-preserving technique and uncontrolled diabetes, as evidenced by HgbA1c >7%, developed gastroparesis. One patient (1%) developed a gastric outlet obstruction caused by a duodenojejunostomy stricture.

Postoperative hemorrhage

Of the seven patients with postoperative hemorrhage, four events occurred within 24 h following TP-IAT, with all attributed to extraluminal bleeding. Six (7%) events were classified as severe. Extraluminal bleeding was localized to the retroperitoneum in four cases – two from the edge of the uncinate process and two from the pancreatectomy and splenectomy bed. One case of extraluminal bleeding had no identifiable source. All five patients with extraluminal bleeding required immediate surgical intervention. Both patients with intraluminal bleeding occurred >24 h after TP-IAT, with one requiring endoscopic clipping and the other having spontaneous resolution.

In the early part of our experience, a pylorus-preserving resection was utilized, with 68% of cases being completed with this technique prior to 2013. The first two cases completed in this cohort had systemic heparin during islet autotransplantation, and one of these patients had an extraluminal postoperative hemorrhage within 24 h. All other cases had heparin mixed into the bags of islet cells and infused into the portal venous system. When evaluating our experience by time, our first 40 cases had a higher rate of postoperative hemorrhage compared with the most recent 40 cases (15% vs 5%, $p = 0.14$).

Table 3 demonstrates the postoperative hemorrhage rates, portal pressures, and IEQ/kg based on heparin dosing groups. A lower median heparin dose was utilized in the <60 units/kg group ($p < 0.0001$). When comparing the postoperative hemorrhage rates by heparin dosing used during islet autotransplantation, there was no difference ($p = 0.97$). Furthermore, although not statistically significant, patients receiving ≥60 units/kg heparin during islet autotransplantation had higher rates of postoperative hemorrhage within 24 h of TP-IAT compared with those receiving <60 units/kg heparin (9% vs 2%, $p = 0.17$). The median aPTT level was higher for those receiving ≥60 units/kg ($p = 0.07$). Maximum portal pressures, ΔPP, and islet cell yields were similar between both groups. Moreover, there was no difference in maximum portal pressures (18 [IQR 16–36] vs 19 [IQR, 14–23] cm H_2O, $p = 0.238$), ΔPP (9 [IQR, 8–22] vs 8 [IQR, 3–11] cm H_2O, $p = 0.13$), islet cell yields (5387 [IQR, 3413–7016] vs 4373 [IQR, 3152–5920] IEQ/kg, $p = 0.40$), or aPTT (90 [IQR, 39–180] vs 89 [IQR, 51–150] secs, $p = 0.95$) in patients with a postoperative hemorrhage compared to those without.

There were no known incidences of PVT. However, there was one patient (1%) with an SMV thrombosis. This patient received 38 units/kg of heparin with 3395 IEQ/kg infused through the splenic vein. Maximum portal pressure was 36 cm H_2O, and ΔPP was 14 cm H_2O. This patient also developed a PE. Lower extremity doppler ultrasound revealed no deep vein thrombosis, and the patient had no known hypercoagulable disorder.

Reoperations

Eight patients (10%) underwent a reoperation within 30 days of TP-IAT, with five being related to postoperative hemorrhage. One patient had an SBO related to a jejunal intussusception and underwent an exploratory laparotomy with reduction of the intussusception. Another patient who had a gastrojejunal feeding tube placed at the time of TP-IAT had a gastrostomy leak on postoperative day 10. This patient was taken back to the operating room for removal of the feeding tube and repair of the gastrostomy site. One patient had a fascial dehiscence and underwent a fascial closure. There was no difference in 30-day reoperation rate based on surgical approach (pylorus-preserving: 13% vs classic: 7%, $p = 0.45$).

Eleven patients (14%) had a reoperation >30 days after TP-IAT. All six patients with an incisional hernia underwent definitive repair. Three patients with an SBO underwent an exploratory laparotomy with lysis of adhesions. One patient with a marginal ulcer underwent an antrectomy with a Roux-en-Y reconstruction. One patient had a presumed SBO and underwent a diagnostic laparoscopy with lysis of adhesions at another institution. Symptoms persisted and imaging revealed a gastric outlet obstruction from a duodenojejunostomy stricture. A resection of the duodenojejunostomy and reconstruction with a Roux-en-Y gastrojejunostomy was performed. There was no statistical difference in the reoperation rate >30 days after TP-IAT based on surgical technique (pylorus-preserving: 19% vs classic: 4%, $p = 0.06$).

Mortality

There was no 90-day mortality. Overall, there were 10 mortalities that occurred at a median of 71 months (IQR, 58–85) after TP-IAT suggesting the devastating nature overall of CP. The cause for two patients (2%) was malnutrition and a failure to thrive. One patient (1%) succumbed to stage 4 lung cancer. One patient (1%) had metastatic pancreatic cancer to the liver identified 6 months after TP-IAT. As this patient had a prior distal pancreatectomy related to chronic pancreatitis with surgical pathology revealing pancreatic intraepithelial neoplasia 3, it is unknown if this was a result of the islet infusion or micrometastases present at the time of TP-IAT. The cause of mortality in six patients (7%) was unknown. While a patient undergoing a pylorus-preserving technique had a higher rate of mortality compared with the classic technique, this was not statistically significant (Table 4, $p = 0.09$).

Discussion

This study evaluated two critical aspects of TP-IAT, surgical technique and intraoperative heparin dosing, to optimize postoperative surgical outcomes. A classic technique with antrectomy led to a reduction in long-term postoperative morbidity, especially with respect to marginal ulcer formation, providing evidence for the universal adoption of this technique. The utilization of a lower heparin dose during islet autotransplantation is deemed to be acceptable, given no apparent increased risk for PVT, and postoperative bleeding is inherently high with any anticoagulation. For surgeons who perform TP-IAT, these findings highlight two potential areas with surgical decision-making to mitigate postoperative complication risk and improve surgical morbidity.

Table 3
Postoperative hemorrhage rates and intraoperative variables by heparin dosing.

	<60 units/kg (n = 44)	≥60 units/kg (n = 32)	p
Heparin infused (units/kg); median [IQR]	52 [47, 57]	66 [63, 72]	<0.0001
Postoperative hemorrhage	4 (9%)	3 (9%)	0.97
aPTT (secs); median [IQR]	78.6 [44.6–133.2]	94.9 [62.8–180]	0.07
Maximum portal pressure during islet infusion (cm H_2O); median [IQR]	18 [13, 22]	21 [16,24]	0.45
ΔPP (cm H_2O); median [IQR]	8 [3, 12]	9 [4, 13]	0.49
Islet cell yield (IEQ/kg); median [IQR]	4049 [2934, 5365]	5697 [4140, 6527]	0.007

Table 4
Mortality.

	Pylorus-preserving (n = 53)	Classic (n = 27)	p
90-day mortality	0 (0%)	0 (0%)	–
Mortality >90 days	9 (17%)	1 (4%)	0.09
Median time interval from surgery; months [range]	71 [8–121]	86 [86-86]	0.38
Causes			0.82
Pancreatic cancer	1 (2%)	0 (0%)	
Lung cancer	1 (2%)	0 (0%)	
Malnutrition	2 (4%)	0 (0%)	
Unknown	4 (8%)	1 (4%)	

Our 30-day morbidity rate of 43% is lower than other studies, with reported rates of 46–58% [18,22,23]. Although there was a higher incidence of bleeding in the pylorus-preserving group, these cases predominantly occurred in the early part of our experience and the bleeding source was mostly extraluminal, so the difference in bleeding between the two groups does not appear to be due to any particular surgical technique. Over time, there have been no changes in the technique or use of energy devices, and hence, these results are likely attributed to the learning curve with the operation. Moreover, while previous studies demonstrated a mean hospital stay of 10–15 days following TP-IAT, our patient cohort had a shorter LOS [18,23,24]. These results can most likely be attributed to the high volume performed at our institution, as well as the learning curve experienced with performing the procedure, and advancements in perioperative care for these patients. In particular, shorter days in the ICU, routine insertion of a nasojejunal tube (eg, corpak) at the time of TP-IAT for early enteral feeding and upon discharge if necessary, and the utilization of a dedicated endocrinology team to manage postoperative blood glucose levels most likely contributed to the shorter LOS observed in this study. Additionally, when evaluating the Clavien-Dindo profile for our patient population, the majority were minor (grade I-II). Most importantly, both a pylorus-preserving and classic technique result in similar 30-day morbidity rates.

The strength of this study was in evaluating the long-term surgical outcomes of TP-IAT to better define the morbidity that can be expected with this operation. Our long-term morbidity rate of 43% is acceptable, and our data demonstrate a mitigation of these postoperative complications with a classic technique. This is most likely attributable to the increased risk of marginal ulceration observed with the pylorus-preserving technique, and the longer follow up with this cohort should not have had an effect on these results. Typically, marginal ulcers occur within 1 year of the operation, and the majority of the classic technique cohort reached this follow up period for an accurate interpretation of the data. While our reported marginal ulcer rate of 15% is similar to other studies with reported rates of 12–18%, it contradicts the study by Barbier et al. by demonstrating an impact of surgical technique on marginal ulcer formation [25–27]. The risk for ulceration is increased in the apancreatic state with an absence of bicarbonate to neutralize acid secretions from the stomach. Furthermore, a component of ischemia with the pylorus-preserving technique can also be a contributory factor, as the gastroduodenal, gastroepiploics, and right gastric arteries are ligated, and the proximal duodenum is being perfused remotely by the left gastric artery. In the classic technique, however, the stomach should be well perfused with the left gastric artery limiting the risk of ischemia, and resection of the antrum eliminates the gastrin producing cells (G cells) in the stomach. Although most ulcers resolve with acid-reducing therapy, significant consequences still exist, such as gastrointestinal hemorrhage, perforation, and intractable ulceration, which can have detrimental effects. Moreover, one patient in our series needed an antrectomy for management. With a standardized postoperative management for all patients in our cohort, including the use of proton pump inhibitors for 3 months, this highlights that the development of marginal ulcers can be prevented technically in TP-IAT. In our experience, ischemia seems to be a more significant factor in causing marginal ulcers after TP-IAT, and hence, we do not feel that longer proton pump inhibitor therapy in these patients would lead to reduced rates. This provides a strong rationale for the universal adoption of a classic technique in reducing morbidity and improving surgical outcomes.

While the risk of morbidity is high with TP-IAT, there is a minimal risk of short-term mortality. Our 90-day mortality rate of 0% is comparable to other studies [18,22,23]. Long-term mortality data is lacking in the literature, and our study was able to better delineate this risk. Although our data does show a trend towards a higher mortality with the pylorus-preserving technique in terms of >30-day mortality, this is most likely related to the longer follow up for this cohort. Overall, long-term mortality risk is low with death occurring years after surgery, highlighting the advancements in surgical and perioperative care for these patients. Unfortunately, one patient in our cohort died from metastatic pancreatic cancer to the liver. While it is unknown if the cause for this metastasis was related to islet infusion or micrometastases present prior to the operation, the development of metastatic pancreatic cancer to the liver 10 months after TP-IAT has been reported [28]. Based on our experience, islet autotransplantation should only be recommended cautiously for patients with high risk lesions, such as intraductal papillary mucinous neoplasms, mucinous cystic neoplasms, or those with high-grade dysplasia. This caution and appropriate informed consent, as in our case, centered around the inability to have pathologic analysis of the resected pancreas prior to islet procurement. Aside from this, malnutrition in this patient population can be challenging and was the most commonly known cause of death in our cohort. Preoperative treatment of patient frailty with prehabilitation programs have shown improvements in postoperative morbidity and mortality after major abdominal surgery [29,30]. This stresses the importance of optimizing preoperative functional performance prior to undertaking this operation and warrants the need for further study into prehabilitation programs for TP-IAT patients.

Islet autotransplantation confers a risk of PVT, with reported rates as high as 4% in some series [18,31]. Yet, this risk has decreased in recent years with improvements in islet preparation [32]. While PVT is a major complication associated with islet infusion, this must be weighed against the risk for postoperative hemorrhage. This presents a dilemma and challenges the surgeon in determining the ideal heparin dose to administer with islet autotransplantation to mitigate both risks. In our practice, we have adopted the utilization of a lower heparin dose nearing 50 units/kg, and this has not increased the risk for PVT. Moreover, although there was no statistical significance most likely related to a low event rate, patients receiving a lower heparin dose had a reduced

rate of postoperative hemorrhage within 24 h of TP-IAT and represents a clinically significant finding. Based on a known short half-life of ~1 h, the administration of intraoperative heparin should theoretically have no effect on bleeding after 24 h. Yet, there are many other contributory factors to the development of postoperative bleeding and PVT that warrant consideration aside from anticoagulation, such as portal pressure and islet volume infused. As ΔPP and pancreatic tissue volume infused are directly correlated, their role in the development of postoperative hemorrhage and PVT have been established [33–35]. Because no patients developed a PVT, this analysis was prevented from being performed in our cohort. Islet cell yield, maximum portal pressure, and ΔPP had no effect on postoperative hemorrhage in our cohort. This suggests that intraoperative heparin dosing may play a larger role than portal pressures and islet volume in the development of postoperative hemorrhage, and our findings provide evidence for the acceptance of a heparin dose <60 units/kg during islet infusion, without impacting the risk for PVT.

There were some limitations to this study. First, this was a single institution study, which could lead to selection bias. Moreover, all operations were performed by experienced hepatopancreatobiliary surgeons at a quaternary care center. Therefore, these results may not be generalizable to every institution. Second, we did not perform routine postoperative imaging to identify PVT, which could have led to an underestimation of portal vein thrombus in a subclinical population. A recent study by Robbins et al. [36] demonstrated a 6.6% PVT rate when screening TP-IAT patients. Furthermore, as seen in the study by Robbins et al. [36], PVT is a self-limited process. Third, routine endoscopy was not employed and could have led to a lower incidence of marginal ulcer. However, the risk of asymptomatic marginal ulcers is low, implying that the results would not have been altered. Fourth, the classic technique could potentially lead to higher rates of bile reflux gastritis and dumping syndrome compared with the pylorus-preserving technique. We did not observe this in our study most likely related to the retrospective nature of the study and the limited follow up in these patients. Lastly, we have previously published our results on islet graft function which was not the focus of this study, but in general any islet cell dysfunction was not felt to be a consequence of heparin dosing.

In conclusion, surgical technique and intraoperative heparin dosing can have clinically relevant impacts on morbidity and mortality after TP-IAT. While a pylorus-preserving technique can have similar surgical outcomes in the short-term, the reduction in long-term morbidity, especially with regards to marginal ulcer formation, provides evidence for the universal adoption of a classic technique to mitigate postoperative complication risk. The utilization of a heparin dose <60 units/kg during islet autotransplantation does not confer an increased risk of PVT and is ideal, given the simultaneous risk of postoperative hemorrhage with anticoagulation. These findings can inform surgeons on ways to optimize TP-IAT surgical outcomes.

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