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Effectiveness of Intraoperative Versus Dedicated Islet Cell Laboratory Isolation for Total Pancreatectomy With Islet Autotransplant

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Background. Total pancreatectomy with islet autotransplantation (TPIAT) requires a complex islet isolation process of the explanted pancreas. Islet isolation has historically required a specialized laboratory to perform islet isolation. We report our experience with a novel technique of intraoperative islet isolation that does not require a specialized islet laboratory, thereby making the isolation process simpler, more accessible, and less costly. **Methods.** We performed a retrospective, comparative effectiveness analysis of 50 adult patients who underwent TPIAT from 2012 to 2020 (TPIAT with remote isolation [n = 20] versus intraoperative isolation of islet cells [n = 30]). The primary outcome was islet equivalents per body weight (IEQ/kg) for patients in each group. **Results.** Mean IEQ/kg's (4294 remote group versus 3015 intraoperative group, $P = 0.06$) and 1-y postoperative C-peptide levels (1.51 ng/mL remote group versus 0.91 ng/mL intraoperative group, $P = 0.10$) were not different between groups. Mean 1-y HbA1c levels (7.7% in the remote group versus 7.1% intraoperative group, $P = 0.67$) and 1-y insulin requirements ($P = 0.31$) were not statistically different. Lower average cost of hospitalization was seen in the intraoperative group, although this was not statistically significant ($104 398 remote versus $78 986 intraoperative, $P = 0.81$). **Conclusions.** Intraoperative islet isolation has similar effectiveness in regard to glycemic outcomes compared with the use of a dedicated islet cell isolation laboratory at a lower cost.

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INTRODUCTION

Chronic pancreatitis is defined as a pathologic fibroinflammatory syndrome of the pancreas in susceptible patients (ie, genetic, environmental, and other risk factors) who develop ongoing pathologic responses to parenchymal injury or stress.[1] Pain is common and is typically the most debilitating symptom for patients, causing a considerable impact on quality of life.[2] Pain associated with chronic pancreatitis is often multifactorial (active inflammation, obstruction of the pancreatic ducts, ischemia of the tissue, nerve damage, etc).[3] Pain management begins with analgesics in a step-up approach; however, treatment options are limited, and patients are often prescribed opioid analgesics for refractory pain.

Surgical techniques including partial resection and drainage procedures have been used in efforts to improve pain, although this improvement is typically transient. Surgical removal of the pancreas can be effective to reduce the abdominal pain; however, removal of the insulin producing beta cells causes subsequent "brittle" diabetes caused by type III-c diabetes. Total pancreatectomy with islet autotransplantation (TPIAT) allows for the hormone producing islets to be isolated and subsequently reinfused to prevent the complications associated with type III-c diabetes. Although TPIAT was initially performed for management of chronic pancreatitis, it has also shown benefit in treatment of recalcitrant recurrent acute pancreatitis.[4]

The process of islet isolation is complex and requires both mechanical and enzymatic digestion of the explanted pancreas. Islet processing has historically required highly specialized facilities that can perform the isolation, thereby limiting its availability. To compensate, surgical centers without processing facilities have collaborated remotely with labs that are capable of islet isolation (ie, shipping the resected pancreas

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offsite for isolation and returning the islet suspension later for infusion). Remote isolation of islet cells has been validated as an acceptable alternative to TPIAT with onsite isolation of islet cells.[5-7] Our institution had initially relied on remote isolation of islet cells and reported comparable rates of long-term insulin and narcotic independence to those who underwent TPIAT with local islet isolation.[5] In 2015, we began to use a novel technique of intraoperative isolation of islet cells first reported by Fan et al[8] from Johns Hopkins University so that we could perform islet isolation without a highly specialized islet cell laboratory.

The aim of this study therefore was to compare the effectiveness of intraoperative versus dedicated islet cell laboratory isolation for total pancreatectomy with islet autotransplant to determine the efficacy of our center's practices. A priori, we hypothesized that intraoperative isolation is comparable to isolation of islet cells at a dedicated laboratory.

MATERIALS AND METHODS

Patient Selection

This was a retrospective cohort study approved by the Dartmouth Committee for the Protection of Human Subjects. Adult patients >18 y old who underwent total pancreatectomy followed by islet cell transplant at Dartmouth-Hitchcock Medical Center from 2012 to 2020 were included in the study. From 2012 through 2015, patients underwent total pancreatectomy with isolation of islet cells at a remote facility 130 miles away. From March 2015 through 2020, patients underwent total pancreatectomy with isolation of islet cells intraoperatively at Dartmouth-Hitchcock Medical Center. Included patients were those who had postoperative data 1 y after TPIAT available. Excluded were patients who underwent partial or completion pancreatectomy.

Surgical Technique

Total pancreatectomy with splenectomy is most often performed as an open technique with a midline laparotomy incision. Attempts are made to keep the pancreas intact through a pancreaticoduodenectomy, and distal subtotal pancreatectomy with splenectomy is often performed with division of the pancreatic neck parenchyma. Care is taken to preserve the gastroduodenal artery (GDA) and splenic artery inflow to the specimen during the resection to minimize ischemia time, preserving pancreas and islet perfusion, making the warm ischemia time negligible. Once the GDA and splenic artery are ligated and divided, the pancreatic head and tail specimens are then removed and passed off of the field and placed immediately into an ice-cold University of Wisconsin (UW) solution or Ringer's Lactate bath that is supplemented with cefazolin. Reconstruction is though a roux-en-Y hepaticojejunostomy with antecolic roux-en-Y gastrojejunostomy anastomosis.

Remote Islet Cell Isolation

Before leaving our facility, the pancreas head and tail specimens were flushed via the GDA and splenic artery stumps with ice-cold UW solution and then submerged in UW solution at 4 °C on ice for ground transport to a remote isolation laboratory 130 miles away at the Massachusetts General Hospital in Boston, MA. Islet isolation was performed through manual intraductal injection of collagenase and protease solutions via 60-cc syringe followed by division of pancreatic parenchyma into 5 to 10 mm pieces and then mechanical digestion using a Ricordi chamber. Purification via COBE cell processor[9] was performed selectively per remote laboratory protocols (for centrifuged pellet volumes >15 mL after digestion). The isolated islet solution was then shipped back to our institution in gas-permeable tissue culture bags in 5% human albumin solution.

Intraoperative Islet Cell Isolation

The islet equipment is brought into the operating room (OR), and the OR air quality is maintained at 15 air changes per hour with high efficiency particulate air filtration and UV germicidal irradiation disinfection per Occupational Safety and Health Administration standards. The head and tail specimens are passed off the surgical field on ice and placed on the back table, where the pancreas is prepared and flushed as detailed earlier. The pancreatic duct is then cannulated and infused with a warm enzyme solution consisting of proteases, collagenase, and buffers to initiate digestion (VitaCyte, Indianapolis, IN). This enzyme solution is then repeatedly injected into the parenchyma using a 60-cc syringe with manual pressure while monitoring for distribution of the enzyme solution throughout the parenchyma. The organ is then divided into small (~5 mm)-sized pieces of tissue manually using scissors. The tissue and enzyme solution is then collected and placed into a Ricordi digestion chamber at 37 °C. As the solution is brought to 37 °C, the chamber is "shaken" to facilitate enzymatic digestion and further mechanical dissociation. All handling of cells is done in the OR using a sterile technique in a biosafety level 2 hood. Samples are taken periodically (every 5 min), and they are stained with dithizone for inspection under the microscope to assess for islet number, size, and morphology. Once digestion is complete, the Ricordi system is cooled to 4 °C. The digest is then collected and mixed with 5% human serum albumin and undergoes a sequence of centrifugations. Purification via COBE processing is not performed regardless of postdigestion volume. To wash the islets, the preparation is resuspended with Hank's balanced salt solution. Finally, the collected cells are suspended with 5% human serum albumin supplemented with 35 U/kg of heparin.

Islet Infusion

Once the prepared islet cells are ready for transplantation into the liver, the patient is given 35 U/kg of heparin intravenously. Using a 12-gauge needle with attached intravenous tubing, the islet cells are infused via gravity directly into the portal venous system via the splenic vein stump. Serial portal pressures are monitored at 5-min intervals throughout the infusion with the infusion held if portal venous pressures reach a change of 20 mmH_2O from baseline or an absolute level of 30 mmH_2O. Heparin infusion is maintained for 72 h postinfusion and titrated to therapeutic heparin unfractionated heparin level (anti-Xa activity).

Statistical Analysis

Continuous variables were evaluated using the Student *t* test and categorical variables using the Fisher exact test. Statistical analysis was performed using Microsoft Excel (Microsoft Corporation, Redmond, WA) and Graphpad QuickCalcs (GraphPad Software Inc, La Jolla, CA). For calculations in which data were not available the denominator was assumed to include all patients (remote, n = 20, and intraoperatively, n = 30). The *P* value for statistical significance was <0.05.

RESULTS

Patient Characteristics

We identified 66 patients who underwent TPIAT at our institution from 2012 through 2020. Fifty-three of these patients underwent total pancreatectomy, whereas 13 underwent either distal pancreatectomy (n = 8) or completion pancreatectomy (n = 5). Three patients were not included given that their surgery had been within the past 4 mo and, therefore, available data were not sufficient for analysis. Of the 50 eligible patients, 20 patients underwent TPIAT with remote isolation, whereas 30 patients underwent intraoperative isolation of islet cells. Comparisons of baseline patient characteristics in Table 1 demonstrate that there were no differences in patient age, body mass index, gender, or type of pancreatitis (ie, chronic versus recurrent acute) between the 2 groups. The "other etiologies" for pancreatitis include hypertriglyceridemia, drug-induced pancreatitis, pancreatic divisum, sphincter of Oddi dysfunction, and annular pancreas.

There were no significant differences in preoperative glycosylated hemoglobin levels ($P = 0.171$) or preoperative fasting C-peptide levels ($P = 0.759$) between the 2 groups. Three of the patients in the remote group were labeled as diabetic (HbA1c > 6.5) preoperatively, and 2 of them were on insulin before the surgery, whereas 1 patient was not on any treatment. Seven of the intraoperative group were listed as diabetic before the surgery, 5 of which were controlled with metformin alone, 1 patient was on insulin, and 1 patient was on both insulin and metformin before their surgery. One patient in the remote group and 5 patients in the intraoperative group had glycosylated hemoglobin levels in the prediabetes range (HbA1c, 5.7–6.4); none of these patients were on any antidiabetic agents.

Primary and Secondary Outcomes

Surgical and islet isolation procedure characteristics between the remote and intraoperative groups are outlined in Table 2. There were no differences in total transplanted islet mass in terms of islet equivalents (IEQs) between the remote and intraoperative groups (310 025 versus 230 478 IEQ, $P = 0.12$). The mean transplanted IEQs per kg patient weight (IEQ/kg) were higher in the remote group, although this did not reach statistical significance (4294 versus 3015 IEQ/kg, $P = 0.06$). There was no statistical difference between the groups in the proportion of patients with transplanted islet mass <2000 IEQ/kg (15% versus 36.7%, $P = 0.35$). A subgroup analysis did not identify any statistical difference in mean transplanted IEQ or IEQ/kg between those with preoperative diabetes or prediabetes or those who were nondiabetic. There was a significant difference in mean transplanted IEQ/kg when comparing preoperative diabetics to nondiabetics within the intraoperative group ($P = 0.03$) but not observed within the remote group ($P = 0.13$). We performed a subanalysis of patients with postdigestion tissue volume >15 mL to compare those who had purification to those who did not have purification (Table 3). We did not appreciate any statistically significant differences between the 2 groups in regard to postoperative complications and primary or secondary outcomes up to 3-y postoperative.

Mean cold ischemia time was significantly lower in the intraoperative group (12 h, 35 min, versus 4 h, 59 min; $P = 0.0001$). Islet cell fluid cultures were positive in 1 of 20 remote patients and 8 of 30 intraoperative patients.

Postoperative fasting C-peptide levels were monitored regularly, and there was no statistical difference in mean levels between the 2 groups at postoperative year 1 ($P = 0.097$), 2 ($P = 0.2$), or 3 ($P = 0.147$). The proportion of patients with 1-y postoperative C-peptide levels <0.5 ng/mL was 12% in the remote group versus 42% in the intraoperative group ($P = 0.07$). A subgroup analysis did not identify any statistical difference in fasting C-peptide levels at 1-y postoperative between those with preoperative diabetes or prediabetes or those who were nondiabetics (Table 2).

Mean glycosylated hemoglobin levels were similar between the groups' postoperative years 1 through 3 (year 1 average HbA1c: 7.7%, remote group, versus 7.1%, intraoperative group; $P = 0.67$). The percentage of patients that were dependent on insulin was not statistically different between the groups' postoperative year 1 ($P = 0.191$), year 2 ($P = 0.750$), or year 3 ($P = 1.0$), nor was a significant difference found in 1-y postoperative insulin dependence in patients with preoperative diabetes or prediabetes or those who were nondiabetics. The Modified auto-Igls criteria were applied using fasting C-peptide levels and HbA1c to further categorize graft function (optimal, good, marginal, and failed). There were no statistical differences found in graft function between the 2 groups when these criteria were applied (Table 4).

Opioid use was assessed at annual visits, and there were no statistical differences between the 2 groups up to 5 y. Mean hospital length of stay was similar between groups (10.9 d versus 11.8 d, $P = 0.44$), as well as 90-d admission rates (8 hospital admissions [40%] versus 14 hospital admissions [46%], $P = 0.565$).

Mean hospitalization cost, defined as the cost incurred to provide the services (which includes costs incurred by the departments providing direct patient care as well as an allocation of the costs of indirect/overhead departments) was higher in the remote group ($104 398 versus $78 986), although this did not reach statistical significance. Causes for 90-d admission included pain control (n = 5), nausea/vomiting (n = 2), skin/wound (n = 2), gastrointestinal bleeding (n = 2), abnormal blood sugar (n = 2), poor oral intake (n = 2), gastric outlet obstruction (n = 1), dislodged J-tube (n = 1), small bowel

TABLE 1.

Patient characteristics	Remote group	Intraoperative group	*P*
Number of patients	20	30	
Age (y) (SD)	40 (10)	43 (14)	0.47
BMI (kg/m^2) (SD)	26.0 (5.6)	27.1 (6.2)	0.76
Sex			0.48
Women, n (%)	12 (60)	20 (67)	–
Men, n (%)	8 (40)	10 (33)	–
Type of pancreatitis			1
Chronic, n (%)	18 (90)	27 (90)	–
Recurrent acute, n (%)	2 (10)	3 (10)	–
Etiology of pancreatitis			0.46
Hereditary, n (%)	7 (35)	15 (50)	–
Idiopathic, n (%)	8 (40)	6 (20)	–
Alcoholic, n (%)	1 (5)	2 (7)	–
Other, n (%)	4 (20)	7 (23)	–
Preoperative HbA1c, % (range)	5.5 (4.6–8.9)	6.0 (4.6–9.6)	0.17
Preoperative fasting C-peptide, ng/mL (range)	3.42 (1.3–6.8)	3.16 (0.8–7.4)	0.76

TABLE 2.

Primary and secondary outcomes	Remote group	Intraoperative group	*P*
IEQ/kg patient weight (mean)	4294	3015	0.06
IEQ/kg (median/ range)	3905/383–10 214	3107/21–8609	
Total IEQ (mean)	310 025	230 478	0.12
Total IEQ (median/ range)	297 100/36 400–854 300	225 289/1473–726 355	
Cold ischemia time, mean (range)	12 h 35 min (9:47–17:30)	4 h 59 min (2:20–7:35)	0.0001
Average cost of hospitalization	$104 398	$78 986	0.81
90-d admission rate (%)	8 (40)	14 (46)	0.57
1-y postoperative patients, n	20	29	
1-y insulin requirement			0.19
Independent, n (%)	9 (45)	5 (23)	–
Dependent, n (%)	11 (55)	17 (77)	–
1-y fasting C-peptide, ng/mL (range)	1.51 (0.1–3.7), n = 17	0.91 (0.1–4.1), n = 19	0.1
C-peptide >0.5 ng/mL	15	11	0.16
C-peptide <0.5 ng/mL	2	8	0.07
Absence of C-peptide testing	3	10	0.33
Insulin therapy with C-peptide >0.5	8	8	1
1-y HbA1c %	7.7 (5.6–11.8), n = 18	7.1 (4.8–11.5), n = 20	0.67
1-y opioid use (y/n)	12-Aug	14/13	0.78
2-y postoperative patients, n	20	26	
2-y insulin requirement			0.75
Independent, n (%)	7 (35)	8 (31)	–
Dependent, n (%)	11 (55)	17 (65)	–
2-y fasting C-peptide, ng/mL (range)	3.6 (0.4–5.3), n = 15	1.2 (0.1–3.7), n = 17	0.2
C-peptide >0.5 ng/mL	12	10	0.44
C-peptide <0.5 ng/mL	3	7	0.5
Absence of C-peptide testing	5	9	0.76
Insulin therapy with C-peptide >0.5	6	2	0.14
2-y HbA1c, %	8.1 (5.4–11.9), n = 19	7.2 (5–11.2), n = 20	0.13
2-y opioid use (y/n)	12-Aug	10-Nov	1
3-y postoperative patients, n	20	20	
3-y insulin requirement			1
Independent, n (%)	6 (43)	4 (41)	–
Dependent, n (%)	12 (67)	9 (69)	–
3-y fasting c-peptide, ng/mL (range)	1.65 (0.1–4.5), n = 13	0.98 (0.1–2.2), n = 12	0.15
C-peptide >0.5 ng/mL	12	7	0.21
C-peptide <0.5 ng/mL	1	5	–
Absence of C-peptide testing	7	8	1
Insulin therapy with C-peptide >0.5	8	3	0.19
3-y HbA1c, %	8.2 (5–11.8), n = 18	7.2 (5.3–10.6), n = 15	0.17
3-y opioid use (y/n)	09-Oct	04-Oct	0.3
Subgroup analysis based on HbA1c %[a]	Remote group	Intraoperative group	*P*
Pre-TPIAT diabetes (n)	3	7	
Prediabetics (n)	1	5	
Nondiabetics (n)	16	17	
IEQ/kg patient weight (mean)			
Pre-TPIAT diabetes	2204	1948	0.83
Prediabetics	4300	1532	–
Nondiabetics	4686	3880	0.31
Pre-TPIAT diabetes vs nondiabetics within each group (*P*)	0.13	0.03	
Total IEQ (mean)			
Pre-TPIAT diabetes	202 133	160 095	0.76
Prediabetics	339 700	103 579	–
Nondiabetics	328 400	288 719	0.52
Pre-TPIAT diabetes vs nondiabetics	*P* = 0.29	*P* = 0.12	
Within each group			

Continued next page

TABLE 2. (Continued)

Primary and Secondary Outcomes	Remote group	Intraoperative group	*P*
1-y insulin requirement	20	29	
Independent			
Pre-TPAIT diabetes, n	0	0	–
Prediabetes, n	0	0	–
Nondiabetics, n	9	5	0.14
Dependent			–
Pre-TPAIT diabetes, n	3	4	1
Prediabetes, n	1	5	0.38
Nondiabetics, n	7	8	0.55
1-y fasting c-peptide, ng/mL	1.51 (0.1–3.7)	0.91 (0.1- 4.1)	0.1
Pre-TPAIT diabetes, n	0.50 (3)	0.57 (3)	0.85
Prediabetes, n	0.5 (1)	0.24 (5)	–
Nondiabetics, n	1.82 (13)	1.31 (11)	0.27
Pre-TPIAT diabetes vs nondiabetics within each group	$P=0.06$	$P=0.31$	
C-peptide >0.5 ng/mL			
Pre-TPAIT diabetes, n	2	2	–
Prediabetes, n	1	1	–
Nondiabetics, n	12	8	0.11
C-peptide <0.5 ng/mL			
Pre-TPAIT diabetes, n	1	1	–
Prediabetes, n	0	4	–
Nondiabetics, n	1	3	0.61
Absence of C-peptide testing			
Pre-TPAIT diabetes, n	0	4	–
Prediabetes, n	0	0	–
Nondiabetics, n	3	6	0.72
Insulin therapy with C-peptide >0.5			
Pre-TPAIT diabetes, n	2	2	–
Prediabetes, n	1	1	–
Nondiabetics, n	5	5	–

[a]Nondiabetes HA1C <5.6, prediabetes HA1C 5.7–6.4, diabetes >6.5. IEQ, islet equivalent; TPAIT, total pancreatectomy with islet autotransplantation.

obstruction (n = 1), sepsis (n = 1), *C. difficile* infection (n = 1), an intra-abdominal abscess (n = 1), and pleural effusion (n = 1). One patient developed a partially occlusive portal venous thrombus, which resolved spontaneously. At the time of data collection, 5 of the 50 patients were found to be deceased (3 from the remote group, 2 from the intraoperative group). Two of the deaths occurred within 6 mo of their surgery (both from the intraoperative group), whereas the others were >2 y post-operation. One patient in the intraoperative group died from acute respiratory distress syndrome in the days following their surgery during the same admission, whereas the other died from sepsis 4 mo postoperation. Causes of death in the remote group included myocardial infarction, sepsis, and renal failure.

DISCUSSION

TPIAT is an effective option for management of refractory pain in patients with chronic or recalcitrant recurrent acute pancreatitis. The process of islet isolation is complex and has historically required highly specialized facilities, limiting its availability. Pancreatic surgical centers without these facilities have sometimes relied on collaborations with remote facilities capable of processing pancreatic tissue. More recently, success has been reported with performing islet isolation intraoperatively without a dedicated islet cell laboratory[8]; however, comparative studies have been lacking. Given that our institution has performed both remote and intraoperative islet cell isolation, we were able to evaluate the comparative effectiveness of these 2 techniques for clinically relevant glycemic outcomes.

The process of islet isolation requires both mechanical and enzymatic digestion of the explanted pancreas with the final product being clusters of islet cells, which can be quantified as IEQ. Islet cell equivalence per kilogram body weight (IEQ/kg) is an essential measure in determination of the amount of transplanted tissue. The ideal number of IEQ/kg is not known, but lower levels have been associated with low C-peptide levels and graft failure.[5,7,8,10-13] We compared IEQ/kg levels between our 2 cohorts, and although the mean total IEQ and mean IEQ/kg were both higher in the remote isolation group, this did not reach a level of statistical significance. Patients with diabetes or prediabetes before TPIAT have been shown to have fewer isolated and transplanted islets and worse metabolic outcomes than preoperative nondiabetics.[14] Similarly, we found that patients with preoperative diabetes yielded lower IEQ than nondiabetic patients, although this was only statistically significant in the intraoperative group. One year fasting, C-peptides were also lower in preoperative diabetics than nondiabetics; however, this was not statistically significant. Bellin et al[10] had reported that IEQ/kg >4000 was the strongest predictor of islet graft function at 10 y in over 200 patients with TPIAT. In our study, 50% of the patients in the remote isolation group and 33% of patients in the

TABLE 3.

Subanalysis of patients with pellet volumes >15 mL

Primary and secondary outcomes	Remote group	Intraoperative group	
Pellet volume of all patients (median/range) (mL)	35 (7–55)	8 (1–60)	
Number of patients with pellet volume >15 mL	15	10	
Purification performed	15	0	
Islet infusion held for increased portal pressure	0/20	5/30	
Subanalysis of pellet volume >15 mL	**Remote group**	**Intraoperative group**	***P***
Preoperative HbA1c, % (range)	5.6 (4.6–8.9)	6.0 (4.8–9.5)	0.48
Preoperative fasting C-peptide, ng/mL (range)	3.87 (1.5–6.8)	2.75 (0.6–5.0)	0.11
IEQ/kg patient weight (mean)	4824	3770	0.47
Total IEQ (mean)	345 827	305 387	0.65
Length of hospital stay, average days (range)	10.3 (6–21)	11.1 (7–16)	0.59
90-d admission rate (%)	5 (33)	7 (70)	0.11
1-y postoperative patients, n	15	10	
1-y insulin requirement			0.35
Independent, n (%)	6 (43)	1 (17)	–
Dependent, n (%)	8 (57)	5 (83)	–
1-y fasting C-peptide, ng/mL (range)	1.68 (0.5–3.7), n = 14	1.9 (0.6–4.1), n = 6	0.69
C-peptide >0.5 ng/mL	14	6	0.12
C-peptide <0.5 ng/mL	0	0	–
Absence of C-peptide testing	1	4	–
Insulin therapy with C-peptide >0.5	8	5	–
1-y HbA1c %	7.9 (5.6–11.8), n = 14	6.6 (4.8–9.5), n = 6	0.17
1-y opioid use (y/n)	6/7	5/2	0.37
2-y postoperative patients, n	15	7	
2-y insulin requirement			0.65
Independent, n	4	3	–
Dependent, n	9	4	–
2-y fasting c-peptide, ng/ml (range)	1.9 (0.4–5.3), n = 11	1.8 (0.2–3.7), n = 7	0.88
C-peptide >0.5 ng/mL	10	5	–
C-peptide <0.5 ng/mL	1	2	–
Absence of C-peptide testing	4	9	–
Insulin therapy with C-peptide >0.5	7	3	–
2-y HbA1c, %	8.5(5.4–11.9), n = 14	7.6 (5–11.2), n = 7	0.41
2-y opioid use (y/n)	6/9	5/2	0.36
3 y postoperative patients, n	15	5	
3-y insulin requirement			1.00
Independent, n (%)	2	1	–
Dependent, n (%)	12	4	–
3-y fasting c-peptide, ng/mL (range)	1.6 (0.4–4.5), n = 11	1.12 (0.1–2.2), n = 5	0.41
C-peptide >0.5 ng/mL	10	4	–
C-peptide <0.5 ng/mL	1	1	–
Absence of C-peptide testing	3	1	–
Insulin therapy with C-peptide >0.5	10	3	–
3-y HbA1c, %	8.7 (5.5–11.8), n = 14	6.8 (5.3–9.2), n = 5	0.09
3-y opioid use (y/n)	6/7	2/2	0.30

IEQ, islet equivalent.

intraoperative group had IEQ/kg >4000 with the mean IEQ/kg for each group being >3000 (4294, remote group, versus 3015, intraoperative group). This lends support to intraoperative isolation being comparable to remote isolation in regard to isolation yield volume.

Transplanted islet graft function is assessed by C-peptide levels and insulin requirements. The international Islet Transplant Registry defines graft failure by stimulated C-peptide levels <0.3 ng/mL[15]; however, stimulated C-peptide levels are not always obtained. In an effort to standardize reporting of islet graft outcomes, the Igls classification has been adopted.[16,17] The modified auto-Igls criteria define graft failure as stimulated C-peptide levels <0.5 ng/mL or fasting C-peptide levels <0.2 ng/mL.[17] Using these criteria, we did not identify any statistical difference in graft failure among the 2 groups at 1 y posttransplant.

The proportion of patients with fasting C-peptide levels <0.2 ng/mL was approximately 18% to 25% in each group in the first 2 y postoperative, which is comparable to larger studies with onsite isolation.[10] Postoperative insulin independence defined as patients not prescribed insulin along with an HbA1c < 6.5 is an additional surrogate of islet cell function. Approximately one-third of patients in each group was insulin independent at 24-mo follow-up, which is comparable

TABLE 4.

Modified auto-Igls criteria

Graft function	Remote	Intraoperative	*P*	
Optimal, n (%)	7 (35)	5 (16.5)	0.51	
Good, n (%)	1 (5)	3 (10)	0.62	
Marginal, n (%)	9 (45)	8 (27)	0.77	
Failed, n (%)	1 (5)	5 (16.5)	0.18	
Not enough data, n (%)	2 (10)	9 (30)		
	Marginal	**Good**	**Optimal**	**Failed**
Remote HbA1c, n (%)[a]	10 (55)	1 (6)	7 (39)	
Intraoperative HbA1c, n (%)[a]	11 (55)	1 (5)	8 (40)	
Remote SHE, n (%)[b]	2 (10)	–	18 (90)	
Intraoperative SHE, n (%)[b]	2 (7)	–	27 (93)	
Remote C-peptide, n (%)	–	–	16 (94)	1 (6)
Intraoperative C-peptide, n (%)[d]	–	–	14 (74)	5 (26)
Remote insulin dose, n (%)[c]	8 (40)	3 (15)	9 (45)	
Intraoperative insulin dose, n (%)[c,d]	10 (45)	7 (32)	5 (23)	

[a]HbA1c: optimal if ≤6.5%, good if <7%, and marginal if ≥7%.
[b]SHE: optimal or good if none and marginal if 1 or more episodes.
[c]Insulin use: optimal if none, good if <0.5 unit/kg/d, and marginal if ≥ 0.5 units/kg/d.
[d]C-peptide: optimal, good, or marginal if stimulated (preferred) or fasting C-peptide positive (>0.5 ng/mL) and failed if negative (≤0.2 ng/mL). Note that C-peptide ≤0.5 ng/mL is the only criterion that can classify the patient as failed.
SHE, significant hypoglycemic event.

to large centers using onsite isolation facilities and other centers using remote isolation facilities.[6,7,10-13,18] Patients who have a fasting C-peptide >0.5 ng/mL but also require daily insulin replacement are considered to have a partial graft function. Partial graft function was similar between the 2 groups at 1-y follow-up (30% versus 31%). The modified auto-Igls criteria can be used to further subdivide graft function into 1 of 4 categories (optimal, good, marginal, and failed) based on C-peptide levels, HbA1c, hypoglycemic events, and insulin requirements. There were no statistical differences in graft function found between the 2 groups when these criteria were applied, confirming comparable graft function with each procedure.

Postoperative graft function correlates with islet cell yield; using this cohort, we previously reported that patients who had >2500 IEQ/Kg were more likely to have well controlled diabetes or only prediabetes at 1 y with low risk of hypoglycemic episodes and minimal glucose variability.[19]

Although we did not appreciate any significant difference in mean hospital length of stay, perioperative mortality, or 90-d admission rates, patients in the intraoperative group had an average hospitalization cost that was approximately $30 000 less expensive. This is secondary to the lack of outside institution isolation fee and transportation of tissue to and from our medical center.

Although this study focused solely on patients who underwent total pancreatectomy, its use can be extrapolated to those undergoing partial and/or completion surgeries as well. In fact, our center has experience expanding the indication for patients undergoing islet cell infusion to include those with benign indications for partial pancreatectomy.[20] At our center, we believe that all patients undergoing pancreatectomy for benign indication should be considered for intraoperative islet cell transplant.

Limitations of the study include its retrospective single-center design and small sample size, which may contribute to type II error. Although the aim of this study was to compare effectiveness of remote islet isolation with intraoperative isolation, we did not have a treatment arm for islet isolation using an "onsite lab" to compare, which most pancreatic surgical centers use. The isolation techniques utilized were similar between the 2 groups with the exception of the islet cell purification step. After digestion, the tissue volume can be purified with COBE processing to decrease pellet volume, which can minimize increases in portal pressures with islet embolization to the liver.[21] There are additional options available for pellet volume reduction such as the unit gravity sedimentation-based "old school" supplementation islet purification technique, which requires minimal islet manipulation.[22] The drawback to purification is the potential to lose viable islet cells, resulting in poorer islet recovery for transplant. The decision to use purification is dependent on the postdigestion tissue volume and was performed in 15 of 20 patients in the remote group for tissue volumes >15 mL. Purification was not performed in any of the patients in the intraoperative group despite postdigestion tissue volumes >15 mL in 10 of 30 patients. Rather, the entire pellet was infused intraportally while portal pressures were monitored. Infusion was briefly held in 5 of 10 of these patients for increased portal pressure per protocol; however, the entire pellet was able to be infused into the portal venous system in each case. If the portal venous pressure were to remain elevated, the remaining pellet may be infused intraperitoneally, which appears to be a safe alternative in patients who do not tolerate the full intraportal infusion, although larger studies are needed.[23] We performed a subanalysis of patients with postdigestion tissue volume >15 mL to compare those who had purification to those who did not have purification. We did not appreciate any statistically significant differences between the 2 groups in regard to postoperative complications and primary or secondary outcomes up to 3-y postoperative. The higher mean IEQ/kg in the remote group could be partially explained by patient selection bias.

Ideally, islet cell isolation would be performed in a dedicated isolation laboratory; however, this technique may not be available to all institutions secondary to their high cost to maintain and their needed expertise. Our study, therefore, demonstrated that intraoperative isolation of islet cells is a viable alternative, comparable for important outcomes at a lower cost.

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