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Preoperative ERCP has no impact on islet yield following total pancreatectomy and islet autotransplantation (TPIAT): Results from the Prospective Observational Study of TPIAT (POST) cohort

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ABSTRACT

Background and aims: Many patients undergoing total pancreatectomy with islet autotransplant (TPIAT) for severe, refractory chronic pancreatitis or recurrent acute pancreatitis have a history of endoscopic retrograde cholangiopancreatography (ERCP). Using data from the multicenter POST (Prospective Observational Study of TPIAT) cohort, we aimed to determine clinical characteristics associated with ERCP and the effect of ERCP on islet yield.

Methods: Using data from 230 participants (11 centers), demographics, pancreatitis history, and imaging features were tested for association with ERCP procedures. Logistic and linear regression were used to assess association of islet yield measures with having any pre-operative ERCPs and with the number of ERCPs, adjusting for confounders.

Results: 175 (76%) underwent ERCPs [median number of ERCPs (IQR) 2 [(Whitcomb et al., 2016 Apr; Kleeff et al., 2017 Sep 7; Machicado and Yadav, 2017; Coté et al., 2018 Jun) 1-41-4]. ERCP was more common in those with obstructed pancreatic duct ($p = 0.0009$), pancreas divisum ($p = 0.0009$), prior pancreatic surgery ($p = 0.005$), and longer disease duration ($p = 0.004$). A greater number of ERCPs was associated with disease duration ($p < 0.0001$), obstructed pancreatic duct ($p = 0.006$), and prior pancreatic surgery ($p = 0.006$) and increased risk for positive islet culture ($p < 0.0001$). Mean total IEQ/kg with vs. without prior ERCP were 4145 (95% CI 3621-4669) vs. 3476 (95% CI 2521-4431) respectively ($p = 0.23$). Adjusting for confounders, islet yield was not significantly associated with prior ERCP, number of ERCPs, biliary or pancreatic sphincterotomy or stent placement.

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Conclusions: ERCP did not appear to adversely impact islet yield. When indicated, ERCP need not be withheld to optimize islet yield but the risk-benefit ratio of ERCP should be considered given its potential harms, including risk for excessive delay in TPIAT.
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Introduction

Chronic pancreatitis (CP) and recurrent acute pancreatitis (RAP) represent a spectrum of disease wherein repetitive inflammatory insults to the pancreas may result in pancreatic atrophy or fibrosis with progressive loss of endocrine and exocrine function [1–3]. Affected patients often suffer from debilitating abdominal pain with narcotic dependence, impaired quality of life, and increased health care utilization, with repeated emergency department visits or hospitalizations [4–8]. Management involves combination of avoidance of alcohol and smoking, pancreatic enzyme replacement therapy, nutritional and endocrine management, comprehensive pain management, and often endoscopic retrograde cholangiopancreatography (ERCP) to relieve obstruction in the main pancreatic duct and the common bile duct [8–10].

When medical and endoscopic therapy fail to mitigate pain associated with CP, surgery, including ductal drainage or parenchymal resection procedures, is considered depending on the morphology [11]. In selected patients, especially those with diffuse small duct disease, with genetic pancreatitis, or who have failed other pancreatic surgeries, total pancreatectomy with islet autotransplantation (TPIAT) is becoming increasingly popular for definitive management of debilitating CP and RAP [7,12]. In TPIAT, the goal of pancreatectomy is to ameliorate pain and restore quality of life, while islet autotransplantation is intended to reduce the burden of post-surgical diabetes [7,13]. Transplanted islet cell mass is the most consistent predictor of short-term and long-term islet graft function and insulin independence [12,14–16]. When feasible, then, it is crucial to avoid procedures that may compromise islet yield, to achieve high islet cell yield for maximal postoperative endocrine function [17]. While prior pancreatic surgery, impaired glycemic control before surgery, and longer duration of disease are all established risk factors for lower islet yield, the impact of antecedent ERCP on islet yield is not clear [12,18–23]. Since TPIAT is becoming more common, an understanding of the potential consequences of prior ERCP on TPIAT outcome is vital as it may impact clinical decision making [17]. While it may be postulated that ERCP with sphincterotomy and stent placement could reduce eventual islet yield by promoting a fibro-inflammatory reaction due to indwelling stents, by inciting post-ERCP acute pancreatitis, or by introducing bacteria into the gland, this has not been explored in a multicenter setting [17].

The POST (Prospective Observational Study of TPIAT) consortium was formed to conduct large volume multicenter research to advance the field of TPIAT and is uniquely positioned to evaluate the impact of pre-operative ERCP [7]. In the POST cohort, we aimed to determine the patient and disease characteristics associated with having an ERCP before TPIAT and its impact on islet yield during TPIAT.

Methods

Study design and participants

This was a retrospective comparative cohort analysis using data collected prospectively by the POST consortium. Participants in the current report underwent TPIAT at 11 US centers between January 2017 and September 2019. The POST study design and enrollment criteria have been previously described [7]. Briefly, patients are eligible for enrollment if they are scheduled for TPIAT (including completion pancreatectomy with IAT) at a participating institution and are willing to consent to participation. All participating centers received approval from their center's institutional review board. Informed consent or parental consent and patient assent were obtained from all participants, as age appropriate.

Patient and disease characteristics

All enrollment sites submitted deidentified data collected using standardized case report forms to a central database managed by the data and coordinating center (DCC) at the University of Minnesota, Division of Biostatistics; the DCC includes a biostatistician, study manager and database manager. Preoperative data included patient demographics, risk factors for pancreatitis, duration of symptoms, time from diagnosis to TPIAT, prior tobacco or alcohol use, prior pancreatic surgery, pre-operative diabetes, exocrine insufficiency, obstructed pancreatic duct, pancreas divisum, and presence of calcifications. Special attention was paid to the number of ERCPs performed and the intervention performed including biliary and pancreatic sphincterotomy, and biliary and pancreatic stent placement.

Islet isolation measures

Each participating institution performed islet isolation according to standard protocols for their clinical site. All sites follow a standard approach of enzymatic digestion followed by mechanical dissociation. However, sites varied in brands of collagenase and neutral protease enzymes used and whether enzyme dosing was standard or adjusted to pancreas features (i.e. fibrosis, calcifications, age). COBE purification was either never performed or performed in a minority of cases when tissue volume exceeded a predefined threshold, depending on the site protocols.

Results of each participant's islet isolation are submitted to the central database and are expressed as [1] islet equivalents (IEQ), a measure of islet mass in which islet count is adjusted by islet diameter (standardized to an islet diameter of 150 μm) and [2] unadjusted islet number, the number of islets not adjusted for size. Body weight in kilograms on day of surgery is also recorded, and islet 'dose' can be calculated as IEQ/kg (islet mass dose) and IN/kg (islet number dose). These 4 measures of islet isolation success – IEQ, IN, IEQ/kg, IN/kg – were considered in the analyses. For most participants, pancreas preservation solution (n = 188) and/or islet product supernatant (n = 222) were sent for sterility testing by culture. Results of both sterility tests were recorded in the POST database qualitatively as positive (indicating bacterial or fungal growth) or negative.

Statistical analysis

The primary research question was whether any ERCP procedures (yes vs. no) or number of ERCP procedures was negatively

(inversely) associated with islet isolation at the time of TPIAT. To understand whether patients who had ERCP differed from those who did not, we first evaluated the association of demographics and disease features with having any ERCPs (yes/no) and with the number of ERCPs.

Categorical characteristics were reported using frequencies and proportions and continuous variables were reported using median and interquartile range (IQR) or mean and standard deviation, as noted. To determine which disease features were associated with ERCP, study groups (ERCP vs. no-ERCP groups) were compared using two-sample t-tests for continuous measures or Fisher's exact test for categorical measures.

We then performed unadjusted linear regression to test for associations between islet yield and ERCP history (i.e., ERCP procedure history (yes/no) and separately the number of ERCP procedures). We then included characteristics significantly associated with ERCP history or number in a multivariate adjusted linear regression model. For this purpose, we implemented forward stepwise regression with a stopping rule based on minimum BIC. For an association of interest, we forced inclusion in the analysis of the ERCP feature being considered (any history or number of ERCPs), along with sex and age (treated as a continuous measure). Because of multiple statistical comparisons, differences were deemed significant at a two-sided $p < 0.01$. Data were analyzed using JMP Pro version 14.0 (SAS Institute Inc., Cary, NC).

Results

Demographic and clinical characteristics of the study cohort

Of the 230 participants included in this analysis, 175 (76%) underwent ERCP [median number of ERCPs (IQR) 2 [1–4]] before TPIAT. Table 1 shows baseline demographic and clinical features for those patients who had any (≥1 ERCP) vs. no ERCPs. Table 2 shows imaging features by MRI/MRCP or CT. Overall the cohort is predominantly female (n = 142, 61.7%), with mean age 31.1 years (SD 16.8, median 30.8 with IQR 15.9–44.4), with children comprising 28.7% (n = 66) of the cohort. The primary indication for TPIAT, as determined by the treating surgical center, was CP in 48.7%, both RAP and CP in 33.9%, and RAP alone in 17.4%.

Pancreatic duct obstruction, surgical history, and disease duration were associated with prior ERCP

For each characteristic that was significantly different between the ERCP and no ERCP groups (in Tables 1 and 2), we then determined how often ERCP was performed in participants with that feature vs those without. Participants with pancreatic ductal dilation or stricture suggesting obstruction by MRI/MRCP or CT were more likely to undergo ERCP (84.1% vs. 64.6% without ductal changes, $p = 0.0009$), as were those with pancreas divisum (93.6% vs. 71.4%, $p = 0.0009$). In contrast, ERCP was less often used in the small subset of participants with idiopathic disease (51.7% vs 79.5% of non-idiopathic, $p = 0.02$). ERCP was also more common in those with prior pancreatic surgery (94.3% vs. 72.8%, $p = 0.005$).

ERCP procedures were associated with longer symptom duration (average increase per 10 years, 1.7 (SE 0.3), $p < 0.0001$) and disease duration (average increase per 10 years, 1.7 (SE 0.4), $p < 0.0001$), imaging features suggesting obstructed pancreatic duct (3.6 (SE 0.3) vs. 2.3 (SE 0.4), $p = 0.006$), and with history of prior pancreatic surgery (4.6 (SE 0.6) vs. 2.8 (SE 0.3), $p = 0.006$). Number of ERCPs was also associated with increased opioid use (0.06 (SE 0.02) more procedures for each 10 mg morphine equivalent per day, $p = 0.004$).

There was a trend towards increased use of ERCP in female patients (81% vs 68.2% of males, $p = 0.04$) and with longer disease duration (OR 1.07 per year, $p = 0.04$), as well as a trend towards more ERCPs performed in females (3.5 (SE 0.3) vs. 2.4 (SE 0.4), $p = 0.04$).

Table 1
Baseline characteristics of the cohort, data expressed as n (%) or as mean (SD). P-values displayed for ERCP any vs none and by linear regression modelling on # of ERCP procedures performed. Significant differences are bolded (defined as p-value <0.01).

	ERCP group (n = 175)	No ERCP group (n = 55)	p-value, ERCP vs no ERCP	p-value, # ERCPs
Sex, Female,	115 (65.7%)	27 (49.0%)	0.038	0.041
Age, mean (years)	31.4 (16.9)	30.3 (16.8)	0.66	0.12
Adult (>18y)	127 (72.6%)	37 (67.3%)	0.49	0.29
Race			0.78	0.067
White	162 (92.3%)	51 (92.7%)		
Black	2 (1.1%)	2 (3.6%)		
Asian	3 (1.7%)	0 (0%)		
Other/Mixed/Unknown	8 (4.6%)	2 (3.6%)		
Ethnicity, Hispanic	16 (9.1%)	3 (5.4%)	0.58	0.59
Risk Factors for RAP/CP (TIGAR-O)				
Obstructive - Pancreas divisum	44 (25.2%)	3 (5.4%)	**0.0009***	0.13
Obstructive - SOD	15 (8.6%)	0 (0%)	0.024	0.25
Obstructive - Other	4 (2.3%)	0 (0%)	0.57	0.71
Toxic/Metabolic	29 (16.6%)	9 (16.4%)	1.0	0.14
Genetic	97 (55.7%)	31 (56.3%)	1.0	0.39
Autoimmune	2 (1.1%)	2 (3.6%)	0.24	0.47
Idiopathic	15 (8.6%)	14 (25.4%)	**0.0022***	0.96
Prior RAP	135 (77.6%)	33 (60.0%)	0.0140	0.89
Average duration of symptoms (y)	8.7 (8.1)	6.5 (5.3)	0.066	**<.0001***
Average duration since diagnosis of pancreatitis (y)	7.4 (7.1)	5.2 (4.9)	0.035	**<.0001***
Prior pancreatic surgery	33 (18.9%)	2 (3.6%)	**0.0046***	**0.0059***
Preoperative exocrine pancreatic insufficiency	55 (31.4%)	16 (29.1%)	0.87	0.04
Preoperative diabetes mellitus	20 (11.4%)	9 (16.4%)	0.35	0.59
Preoperative hemoglobin A_{1c}, mean, (%)	5.7 (1.2)	5.7 (1.0)	0.66	0.26
Preoperative insulin dose, mean, units/d	3.0 (11.6)	9.4 (43.8)	0.16	0.26
Preoperative daily morphine equivalents, mean, mg/d	52.4 (107.0)	40.0 (74.8)	0.42	**0.0043***

Table 2
Imaging features by MRI/MRCP and CT scan prior to TPIAT by ERCP history.

MRI/MRCP	ERCP Group (n = 151)	No ERCP Group (n = 51)	p-value, ERCP vs no ERCP	p-value, # ERCPs
MRI - Atrophy	57 (37.7%)	18 (35.3%)	1.0	0.50
MRI - Irregular, strictured or dilated pancreatic duct	94 (62.3%)	19 (37.3%)	0.011	**0.0038***
MRI - Calcifications	16 (10.6%)	4 (7.8%)	0.78	0.94
CT Scan	**ERCP Group (n=149)**	**No ERCP Group (n=48)**		
CT - Atrophy	43 (28.9%)	14 (29.2%)	1.0	0.062
CT - Dilated pancreatic duct	60 (40.3%)	10 (20.8%)	0.015	0.023
CT - Calcifications	56 (37.6%)	11 (22.3%)	0.080	0.090
Combined MRI/MRCP and CT data, Feature on either study:	**ERCP Group (n=173)**	**No ERCP Group (n=55)**		
Atrophy	80 (46.2%)	25 (45.4%)	1.0	0.19
Pancreatic ductal changes	111 (64.2%)	21 (38.2%)	**0.0009***	**0.0059***
Calcifications	61 (35.3%)	13 (23.4%)	0.14	0.24

Abbreviations: MRI/MRCP = magnetic resonance imaging with magnetic resonance cholangiopancreatography CT = computed tomography.

Prior ERCP procedures did not appear to impair islet isolation outcomes

There was no difference in islet isolation outcomes between those who underwent ERCP procedures vs those who did not in either adjusted or unadjusted regression analyses. In the ERCP group, mean total IEQ isolated for transplant was 238,284 (SE 12,882) vs 241,529 (SE 23,473) in the non ERCP group [for unadjusted regression analysis ($p = 0.90$) and for adjusted regression analysis ($p = 0.31$)] and IEQ/kg was 4145 (SE 266) vs 3476 (SE 484) [for unadjusted regression analysis ($p = 0.23$) and for adjusted regression analysis ($p = 0.09$)] respectively. Similarly, no differences were found between those who did vs. did not undergo pancreatic duct sphincterotomy, pancreatic duct stenting, biliary sphincterotomy, or biliary duct stenting (Table 3). The number of ERCPs performed was not associated with IEQ ($p = 0.29$), IEQ/kg ($p = 0.47$), islet number (IN) ($p = 0.09$) or IN/kg ($p = 0.17$). The apparent trend towards correlation between number of ERCPs and IN is lost if two outlier participants with 20 and 25 ERCPs are removed from the dataset ($p = 0.39$). Likewise, there was no association of number of ERCPs with islet isolation outcomes when adjusted for potential confounders in multivariate regression modelling.

Microbial contamination of islet product and pancreas preservation solution was more common with prior ERCP.

Among participants with a prior history of any ERCP, the islet product was culture positive in 41.8% versus 13.5% of those with no history of ERCP ($p = 0.0001$); pancreas preservation solution was culture positive in 62.0% versus 36.8% respectively ($p = 0.006$). Those with a positive islet culture had an average of 4.59 (SE 0.40) prior ERCPs while those with a negative culture had 2.28 (SE 0.37; $p < 0.0001$). Those with a positive pancreas preservation solution culture averaged 4.08 (SE 0.37) prior ERCPs compared to 2.48 (SE 0.42) in those with culture negative pancreas preservation solution ($p = 0.004$).

Discussion

Management for RAP and CP remains challenging and a multidisciplinary step-up approach is recommended for pain management [24]. Initial conservative management includes life style modifications (e.g. cessation of smoking and alcohol use), dietary adjustments, pancreatic enzyme replacement therapy, and optimization of pain medication. If pain is refractory to appropriate conservative measures, interventional endoscopy or surgery is pursued [9,25]. With the advent and refinement of islet autotransplantation to prevent post-surgical diabetes, TPIAT is increasingly pursued with cautious optimism. As a part of the step-up approach, many eventual TPIAT candidates often undergo ERCP for CP or RAP aiming to alleviate symptomatic pancreatic ductal obstruction to relieve pain caused by intraductal hypertension, or empiric biliary/pancreatic sphincterotomy to prevent recurrent attacks of AP. However, impact of pre-operative ERCP on islet yield following TPIAT has not been previously addressed in a multicenter setting. We hypothesized that ERCP might reduce islet yield by exacerbating intrapancreatic inflammation and damage or by prolonging time to TPIAT. Understanding the impact of ERCP on TPIAT is crucial to optimizing TPIAT patient selection and timing.

Table 3
Islet isolation outcomes expressed as unadjusted mean (SE) by ERCP intervention status, p-values for unadjusted/adjusted regression analyses reported.

Procedure Performed	Total IEQ		p-value	Total IN		p-value	IEQ/Kg		p-value	IN/Kg		p-value
ERCP			0.90/0.31			0.77/0.78			0.23/0.09			0.29/0.08
Yes	238,284	(12,882)		271,951	(14,207)		4145	(266)		5144	(361)	
No	241,529	(23,473)		280,677	(25,887)		3476	(484)		4364	(658)	
PD stent			0.38/0.91			0.32/0.16			0.51/0.52			0.63/0.65
Yes	231,354	(14,207)		264,423	(15,663)		4108	(294)		5078	(400)	
No	252,095	(18,523)		290,201	(20,422)		3790	(384)		4758	(521)	
Biliary stent			0.41/0.36			0.37/0.53			0.33/0.68			0.24/0.86
Yes	213,276	(33,144)		243,406	(36,550)		3365	(686)		3926	(930)	
No	242,407	(11,991)		277,971	(13,223)		4072	(248)		5095	(336)	
PD sphincterotomy			0.24/0.51			0.95/0.89			0.86/0.92			0.20/0.34
Yes	226,247	(15,563)		273,152	(17,223)		4029	(323)		5347	(437)	
No	253,065	(16,301)		274,868	(18,040)		3947	(339)		4535	(458)	
Biliary sphincterotomy			0.42/0.50			0.88/0.18			0.71/0.20			0.33/0.15
Yes	253,364	(21,048)		276,898	(23,251)		3854	(436)		4477	(591)	
No	233,267	(13,355)		272,792	(14,753)		4045	(277)		5154	(375)	

Abbreviations: IEQ = islet equivalents, IN = islet number, IEQ/kg = islet equivalents per kg body weight, IN/kg = islet number per kilogram body weight.

Reassuringly, we found no adverse impact of ERCP on islet isolation outcomes in 230 consecutive patients in the POST cohort. Our study provides a more robust confirmation of an earlier single-center study that suggested ERCP history in the 2 years before TPIAT did not adversely impact islet isolation [14]. In this earlier study from Medical University of South Carolina, 105 patients who underwent ERCP within 2 years of TPIAT had similar IEQ/kg isolated compared with 62 patients who did not undergo ERCP. The current multicenter study was more rigorous as data collection was prospective, captured more patients and incorporated data on all ERCP procedures (not limited to 2 years), and explored the impact of number of ERCPs and type of intervention, i.e., biliary/pancreatic sphincterotomies, biliary/pancreatic stent placement. Besides evaluating IEQ and IEQ/kg, which are the most common isolation metrics reported and reflect islet mass, we also collected islet number (IN and IN/kg) not adjusted for mass. Transplanted islet cell mass and number are the most consistent predictors of short-term and long-term islet graft function [12,14,15,26]. Reassuringly, none of our 4 measures of islet isolation success were negatively associated with having prior ERCP or with the number of prior ERCPs. Along with the earlier single-center study, our study further affirms that theoretical ERCP-induced fibrosis, contamination of pancreas gland with possible gut microbes, and other potentially detrimental mechanisms of ERCP do not seem to have a clinically important impact on islet autotransplantation [17]. Thus, when ERCP is indicated in RAP and CP, it need not be withheld solely for the purpose of optimizing diabetes outcomes after TPIAT outcomes [17].

We did note, however, that microbial contamination of the islet product or pancreas preservation solution was more common in those with an ERCP history and was associated with number of ERCPs performed. This is likely a consequence of instrumentation of the pancreas and sphincterotomy during ERCP posing a risk for secondary infection of the pancreatic and biliary tract and has been previously reported [27]. While specific protocols differ between centers, it is common practice to administer prophylactic antibiotics during and after TPIAT and to extend treatment with appropriately tailored antimicrobials when cultures are positive. In this context, multiple prior studies have suggested minimal adverse impact on infection risk of culture-positive islet product or pancreas preservation solution [27–29]. Although two studies have suggested higher rates of islet graft failure with positive cultures, this was more likely explained by low islet yield in these same patients, without clear direct relationship to the positive cultures [27,30].However, one might consider these risks when determining if ERCP in warranted in a patient who is likely to proceed to TPIAT.

In our study, more than three-fourth of patients underwent ERCP, with a median of two ERCPs before TPIAT. Utilization of endoscopic procedures in our cohort was slightly more than the 61% utilization of therapeutic ERCP reported in the multicentered adult NAPS2 consortium and the 66% reported in the pediatric INSPPIRE consortium [31,32]. The higher utilization of endoscopic procedures is consistent with the multi-disciplinary step-up management algorithm generally adopted in pancreas centers of excellence, i.e., medical therapy followed by endoscopic therapy and then surgical treatment for CP [24]. As may be expected, ERCP was more likely to be performed in those with signs of an obstructive pancreatic duct and pancreas divisum, traditionally likely candidates for pancreatic endotherapy. The remaining TPIAT patients who did not undergo preoperative ERCP were possibly those with small duct disease in which decompression is not feasible, those with RAP and no ductal obstruction, or those with hereditary pancreatitis in whom TPIAT was not delayed because of concerns for unnecessarily prolonging disease and duration of pain. However, it should be noted that among those who underwent ERCP, only a modest number of procedures were performed. This could be partly attributed to a referral bias, since this study was conducted in 11 of the most active centers for TPIAT in United States. Fewer than 25% of participants had more than 4 ERCPs, so we may not be adequately powered to determine if a very large number of ERCPs carries an adverse prognosis, as there is a positive correlation between duration of pancreatitis and number of ERCPs.

However, there remains a concern that repetitive ERCP interventions may be associated with deleterious *pain* outcomes when surgery is eventually performed [33]. Multiple ERCPs with sphincterotomies and/or repetitive stenting (>3) have been reported as predictors for persistent pain and prolonged narcotic use after TPIAT [14]. Repetitive ERCPs with stenting has a potential to induce iatrogenic CP which some experts believe may increase risk for central sensitization and suboptimal pain outcomes after TPIAT [34,35]. Thus, although our current analyses have focused only on the impact on islet yield, physicians should also consider at least theoretical risks for central sensitization and hyperalgesia if considering repetitive ERCPs to substantially delay TPIAT [18,26]. In our cohort, we observed that a greater number of ERCPs was associated with a higher daily opioid use at pre-surgical assessment prior to TPIAT maybe indicating a more significant disease burden. Thus, the risk-benefit ratio of every ERCP should be thoughtfully considered in a multi-disciplinary setting, and individualized based on patient's clinical scenario. The POST study is ongoing and will be able to directly address the impact of antecedent ERCP on pain outcomes in the future.

This study has some noteworthy limitations. First of all, it was performed in 11 major tertiary referral centers that offer TPIAT. POST is an ongoing prospective study with a goal of accruing 450 recipients, and these results are based on an interim analysis. As a result, this interim analysis may have less statistical power to reach definite conclusions on risk of ERCP, and data on islet graft failure and on post-operative insulin requirement will be available only at the study's completion. However, prior studies suggest that islet graft failure or success is highly tied to islet mass transplanted [16,26]. The mean islet equivalent per kilogram body weight in our ERCP cohort was 4145 IEQ/kg which could signify sustained islet graft function, but complete follow up data will be needed to draw effective conclusions on long term diabetes outcome. Islet isolation protocols are generally similar across centers but differ in specifics of enzyme brand, enzyme dosing, and purification for high tissue volume, which may introduce variability in islet yields. Some of the ERCPs were performed at outside institutions and severe adverse events related to these ERCPs that could impact islet yield (i.e. severe acute pancreatitis secondary to ERCP) were not available in POST, nor were details on stent diameter or time of indwelling stents. We did not perform sub-analyses for specific patient populations (obstructive disease, genetic disease), but future studies on the impact of ERCP in post TPIAT pain and diabetes outcomes may consider whether impact of ERCP differs based on disease mechanisms.

In summary, this study represents the largest cross-sectional assessment of the impact of prior ERCP on islet cell yield after TPIAT. The study is unique in that it is a multicenter study located in the United States and includes carefully collected data on a large number of patients managed in a multidisciplinary setting by experts in CP. Our conclusions suggest that pre-operative ERCP does not have a detrimental impact on islet cell yield at the time of TPIAT. When indicated, ERCP need not be withheld to optimize islet yield, but the risk-benefit ratio of this procedure should always be weighed given its potential harms, including risk for excessive delay in TPIAT with potential negative impact on pain and quality of life outcomes.

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MA, DA, SA, AB, GB, SC, DC, MF, TG, BH, VK, LL, LS, RM,KM, JN,BN, AP,TP, SS,VS, KS,MW, PW- critical revision of the manuscript.

Declaration of competing interest

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