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# Prevalence and predictors of pain and opioid analgesic use following total pancreatectomy with islet autotransplantation for pancreatitis

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ABSTRACT

*Background & objectives:* Total pancreatectomy with islet autotransplantation (TPIAT) is employed for the management of refractory pain in chronic pancreatitis (CP) with the prospect of partial beta cell preservation. The primary aim of this study is to evaluate the prevalence and predictors of abdominal pain and opioid use following TPIAT.
*Methods:* A single center cohort study of all adult patients who underwent TPIAT from 2011 to 2015 for CP. Postoperative pain outcomes included: opioid use, ongoing abdominal pain and new characteristic abdominal pain. Multiple logistic regression analysis was used to evaluate known and potential predictors of postoperative pain outcomes.
*Results:* During the study period, 46 patients underwent TPIAT. Following surgery, 89% of patients had resolution of their pre-operative abdominal pain; however, 83% of patients developed a new characteristic abdominal pain. Opioid independence was achieved in 46% of patients. Acute recurrent pancreatitis (ARP) (OR: 11.66; 95%CI: 1.47–92.39; $p = 0.02$) but not pain duration >3 years or $\geq$ 5 ERCPs was independently associated with resolution of pre-operative abdominal pain on multiple logistic regression. None of these factors were associated with cessation of opioid use.
*Conclusion:* While the majority of patients have resolution of their initial abdominal pain following TPIAT, many will also develop a new characteristic abdominal pain and only half of all patients achieve opioid independence. ARP is the only independent factor associated with positive postoperative pain outcomes and should be considered a standard criterion for patient selection.


## 1. Introduction

The abdominal pain of chronic pancreatitis (CP) has profound effects on patients suffering from the disease, with a diminished quality of life similar to that of patients with advanced lung, heart, kidney and liver diseases [1–3]. Pain is present in up to 90% of CP patients and is the most challenging aspect in the clinical management of these patients, as the current arsenal of therapies are limited and lack long-term efficacy [4].

Total pancreatectomy (TP) for the management of pain in CP is commonly reserved for those patients in whom other therapeutic options for managing pain have failed. The concept of performing a simultaneous autologous islet autotransplant (IAT), referred to as total pancreatectomy with islet autotransplantation (TPIAT), was

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first described in 1977 as a means of preserving beta cell mass to forestall the development of insulin dependent diabetes following surgery [5]. This procedure has become increasingly popular in North America over the last decade with several recently published series from different centers reporting variable pain outcomes [6–10]. According to these series, the majority of patients have persistent abdominal pain after months to years of follow-up despite the complete removal of the pancreas. Opioid use has been proposed as a selection criteria for this surgery; however, ongoing opioid use has been reported to be as low as 30–40% and as high as 67–70% following TPIAT. Given these reported pain outcomes following TPIAT, it appears that certain selection criteria for this procedure are suboptimal.

The primary aim of this study was to report the prevalence of post-operative abdominal pain, opioid use and the development of a new characteristic abdominal pain. The secondary aim was to evaluate the factors associated with resolution of abdominal pain and ongoing opioid use.

## 2. Methods

### 2.1. Study design, population and data collection

The study was approved by the Johns Hopkins Institutional Review Board for Human Research and complied with Health insurance Portability and Accountability Act (HIPPA) regulations.

This is a single center cohort study of all adult patients who underwent TPIAT at the Johns Hopkins Hospital from August 2011 to September 2015 for CP. Patients were identified through a prospectively maintained institutional database of patients undergoing TPIAT. Clinical and imaging variables were obtained from both the prospective database and through a review of the medical records.

### 2.2. Indication for TPIAT

All patients were evaluated in the multidisciplinary pancreatitis clinic prior to surgery. All relevant medical records and abdominal imaging from referring institutions were obtained and reviewed. Patients were selected for surgery based on the presence of severe chronic abdominal pain (>6 months) associated with CP that had not responded to medical, endoscopic or prior surgical therapy that was associated with a significant impairment in the patients quality of life. The medical pancreatologist (V.K.S) and treating surgeons (M.A.M and K.H.) all had to agree that each patient's pain was disabling enough to warrant TP and the endocrinology team (RRK, EH) evaluated patients for IAT.

### 2.3. Definition of variables

All patient reported episodes of AP were either confirmed or refuted by obtaining and reviewing the medical records from the time of the reported episode of AP to ensure they meet the revised Atlanta classification criteria for AP [11]. ARP was defined as $\geq$ two episodes of AP. Patients were classified as having CP if they had abdominal pain >6 months with either severe or moderate criteria for CP according to the M-ANNHEIM classification and/or if they had prior or ongoing ARP [12,13]. A dilated main pancreatic duct (MPD) was defined as a duct that was $\geq$ 5 mm on endoscopic ultrasound (EUS) or MRCP. The number of EUS criteria for CP were recorded (five parenchymal and four ductal criteria) [14]. High risk alcohol consumption for AP or CP and an ever smoker were defined according to definitions utilized in the North American Pancreatitis Study 2 [15]. A gene mutation positive patient was defined as pathogenic variant (s) identified in any of the 4 following genes: PRSS1, CFTR, CTRC and SPINK1. Pathogenic gene variants were defined in accordance to http://cftr2.org and http://pancreasgenetics.org/index.php databases.

The pain outcomes variables following surgery were defined as follows: 1) Complete resolution of pre-operative abdominal pain; 2) Ongoing opioid use: persistent opioid use >3 months following surgery; 3) Development of new characteristic abdominal pain: patient reported that they developed a new abdominal pain that was different with regards to location and character compared to their pre-operative abdominal pain; and 4) Partial improvement in

**Table 1**
Demographic and clinical details of cohort undergoing total pancreatectomy and islet autotransplant, based on resolution of pre-operative abdominal pain.

| | Total (N = 46) | Persistent abdominal pain (N = 8) | Resolution of abdominal pain (N = 38) | *p* |
|---|---|---|---|---|
| *Demographic details* | | | | |
| Median age at surgery (IQR) | 44.8 (35–50.7) | 46.1 (36.5–57.9) | 44.8 (28.2–50.6) | 0.43 |
| Female sex (n) | 27 (59%) | 6 (75%) | 21 (55.3%) | 0.30 |
| Race | | | | 0.41 |
| White (n) | 43 (94%) | 8 (100%) | 35 (92.1%) | |
| Black (n) | 3 (7%) | 0 (%) | 3 (7.9%) | |
| *Etiological factors for Pancreatitis* | | | | |
| Pathogenic Gene mutation (n) | 18 (39%) | 3 (37.5%) | 15 (39.5%) | 0.92 |
| History of heavy or very heavy alcohol consumption (n) | 11 (24%) | 2 (25%) | 9 (23.7%) | 0.94 |
| Ever smoker (n) | 15 (33%) | 3 (37.5%) | 12 (31.6%) | 0.75 |
| Pancreas divisum (n) | 10 (22%) | 2 (25%) | 8 (21%) | 0.81 |
| History of recurrent acute pancreatitis (n) | 37 (80%) | 4 (50%) | 33 (86.84) | 0.02 |
| *Imaging features of chronic pancreatitis* | | | | |
| Pancreatic duct enlargement (>5 mm) (n) | 10 (22%) | 1 (12.5%) | 9 (23.7%) | 0.49 |
| Calcifications on CT (n) | 17 (37%) | 2 (25%) | 15 (39.5%) | 0.44 |
| EUS score $\geq$ 3 | 41 (89%) | 7 (88%) | 34 (89%) | 0.87 |
| *Preoperative clinical details* | | | | |
| > 3 years from first symptoms to TPIAT (n) | 33 (72%) | 5 (62.5%) | 28 (73.7%) | 0.52 |
| Opioid use prior to TPIAT (n) | 38 (83%) | 8 (100%) | 30 (78.9%) | 0.153 |
| Neuropathic pain medication use prior to TPIAT (n) | 16 (35%) | 5 (62.5) | 11 (28.9%) | 0.07 |
| Prior pancreatic surgery (Whipple, Puestow or Frey) (n) | 5 (11%) | 2 (25%) | 3 (7.9%) | 0.16 |
| History of comorbid Depression or Anxiety (n) | 23 (50%) | 8 (100%) | 25 (65.79%) | 0.051 |
| *Laparoscopic TPIAT* | 18 (39%) | 4 (50%) | 14 (36.9%) | 0.49 |

EUS: Endoscopic ultrasound; IQR: Interquartile range; TPIAT: total pancreatectomy and islet autotransplant.

**Table 2**
Pain outcomes following TPIAT (n = 46).

| | N (%) |
|---|---|
| Opioid independence. | 21 (46%) |
| Median time to Opioid independence in weeks, n = 21 (IQR). | 30.1 (8.3–66.6) |
| Resolution of pre-operative abdominal pain. | 38 (83%) |
| Resolution or improvement in pre-operative abdominal pain. | 41 (89%) |
| Development of new characteristic abdominal pain. | 38 (83%) |
| Duration of new characteristic? abdominal pain | |
| <6 months. | 11 (24%) |
| ≥ 6 months to < 1 year. | 8 (17%) |
| ≥ 1 year. | 19 (41%) |

abdominal pain: ≥ 50% reduction in pain as measured before and after TPIAT based on a visual analog scale.

## 3. Stastical analysis

Continuous and categorical data were compared between groups using standard parametric and non-parametric testing where appropriate. Two separate multiple logistical regression models were used to predict 1) resolution of pre-operative abdominal pain and 2) ongoing opioid use. Variables were chosen for selection in these multiple logistical regression models based on data from previously published studies evaluating pain outcomes in patients undergoing pancreatic surgery for CP which include ERCP, duration of pain etc. and a combination of forward and backward stepwise logistic regression, where variables with a p value of <0.2 were removed from the model in a stepwise process [6,16–19]. The results are presented as estimated odds ratios (OR) with respective 95% confidence intervals (95% CI) and *p* values. A two-sided p-value of <0.05 was considered statistically significant. All statistical analyses were performed using STATA version 13 (College Station, TX, U.S.A.).

## 4. Results

### 4.1. Description of cohort

A total of 46 patients underwent TPIAT during the study period. The clinical details of the cohort are presented in Table 1. The median age at surgery was 44.8 years (IQR: 35–50.7), 59% were female and 94% were white. Regarding the etiological factors associated with ARP and CP, 18 (39%) patients had identified pathogenic gene variants (s), 11 (24%) had a history of high risk alcohol consumption, and 15 (33%) had a history of smoking. There were 37 (80%) patients with a history of ARP.

### 4.2. Pain outcomes

The median (IQR) follow up, at which the postoperative pain was evaluated, was 1.17 years (0.72–1.92 years). At the time of last follow up, 41 (89%) patients had resolution of pre-operative abdominal pain that had been attributed to CP (Table 2). However, 38 (83%) patients developed a new characteristic abdominal pain. This new characteristic abdominal pain was pervasive in nature, lasting <6 months in 11 (24%) patients, ≥ 6 months to < 1 year in 8 (17%) patients and ≥ to 1 year in 19 (41%) patients. Opioid independence was achieved in 21 (46%) patients at the time of last follow-up with a median time to opioid independence of 30.1 weeks (IQR: 8.3–66.6 weeks).

A comparison of patients with and without resolution of pre-operative abdominal pain at follow up is presented in Table 1. Patients with resolution of pre-operative abdominal pain were more likely to have a history of prior or ongoing ARP (86.84% vs 50%, p = 0.02). Patients without resolution of pre-operative abdominal pain were more likely to have used neuropathic pain medication prior to surgery, but this did not reach statistical significance (62.5% vs 28.9%, p = 0.07). There were no differences in any other baseline demographic factors, etiological factors, imaging features of CP or preoperative clinical characteristics between the two groups.

### 4.3. Predictors of pain outcomes

On the univariable analysis to evaluate predictors for resolution of pre-operative abdominal pain, only ARP (OR: 6.6; 95%CI: 1.24–35.23; p = 0.03) and not pain duration ≥ 3 years (OR: 1.68; 95%CI: 0.32–8.35; p = 0.53) or ≥ 5 ERCPs (OR: 2.77; 95%CI: 0.46–16.20; p = 0.26) was associated with resolution of pre-operative abdominal pain (Table 3). On multivariable analysis only ARP (OR: 11.66; 95%CI: 1.47–92.37; p = 0.02) was associated with resolution of pre-operative abdominal pain.

On univariable and multivariable analysis of factors associated with continued opioid use following TPIAT, neither ARP, pain duration ≥3 years nor ≥5 ERCPs were associated with continued opioid use (Table 4).

The number of ERCPs and time from symptom onset were assessed as continuous independent variables in the multivariable analysis but neither were associated with resolution of pre-operative abdominal pain or continued opioid use (p > 0.05 for both outcome variables).

## 5. Discussion

Appropriate patient selection for TPIAT is paramount to ensure the best possible outcomes for this morbid procedure. The primary finding of this study is that nearly one half of patients have ongoing opioid use following TPIAT and despite 89% of patients having

**Table 3**
Univariable and multivariable analysis for predicting resolution of pre-operative abdominal pain.

| Clinical predictor | Univariable | | Multivariable[a] | |
|---|---|---|---|---|
| | OR (95%CI) | *p-value* | OR (95%CI) | *p-value* |
| History of prior or ongoing Recurrent Acute Pancreatitis | 6.60 (1.24–35.23) | 0.03 | 11.66 (1.47–92.37) | 0.02 |
| Duration of Pain ≥3 years | 1.68 (0.32–8.35) | 0.53 | 0.45 (0.05–3.96) | 0.47 |
| ≥5 ERCPs | 2.77 (0.46–16.50) | 0.26 | 3.35 (0.44–25.46) | 0.24 |

CI: Confidence interval; ERCP: Endoscopic retrograde cholangiopancreatography; OR - Odds Ratio.
[a] Each clinical predictor was adjusted for the other clinical predictors listed above.

**Table 4**
Univariable and multivariable analysis for predicting continued opioid analgesic use following TPIAT.

| Clinical predictor | Univariable | | Multivariable[a] | |
|---|---|---|---|---|
| | OR (95%CI) | *p-value* | OR (95%CI) | *p-value* |
| History of Recurrent Acute Pancreatitis | 0.27 (0.05–1.47) | 0.13 | 0.33 (0.24–2.07) | 0.054 |
| Duration of Pain ≥3 years | 0.66 (0.18–2.46) | 0.54 | 0.78 (3.37–0.74) | 0.18 |
| ≥5 ERCPs | 1.24 (0.68–2.24) | 0.48 | 1.22 (2.63–0.61) | 0.57 |

CI: Confidence interval; ERCP: Endoscopic retrograde cholangiopancreatography; OR - Odds Ratio.
[a] Each clinical predictor was adjusted for the other clinical predictors listed above.

resolution of pre-operative abdominal pain, 83% unfortunately developed new characteristic abdominal pain. This study also found that a history of ARP was the only preoperative predictor for resolution of pre-operative abdominal pain following TPIAT.

Opioid analgesic use is ubiquitous among patients with CP in the United States, with the majority of adult patients on opioids at the time of TPIAT [6–10]. Given that refractory chronic abdominal pain resulting in opioid use is commonly used as a criterion for selecting patients for TPIAT, cessation of opioids should be the primary endpoint assessed when evaluating pain outcomes following TPIAT as opposed to changes in oral morphine equivalents and/or pain scales such as the visual analog score (VAS) or Izbicki [20]. Using changes in oral morphine equivalents is unreliable as a pain outcome due to the high variability in prescribing practice, with many patients using as needed opioids, making it impossible to calculate cumulative opioid use unless it is recorded on a daily basis by patients [21]. In addition, equianalgesic tables used to generate oral morphine equivalents are inconsistent with variable conversion ratios likely due to the high variability in the pharmacokinetics of opioids in individual patients [22]. Ongoing opioid use is associated with a host of deleterious effects: tolerance; opioid-induced bowel dysfunction that can result in the development of distinct chronic abdominal pain syndrome; and finally but most importantly, opioid induced hyperalgesia [23]. Commensurate with prior studies, opioid independence in this study was achieved in 46% of patients at a median follow up of 1.17 years, which can be viewed as disappointing for a morbid surgery. These poorer than expected outcomes are likely the result of two major factors. Firstly, the central sensitization that occurs in CP that is augmented by opioids [24–26]. Secondly, patient selection based simply on the presence of chronic abdominal pain as well as morphologic changes of the pancreas on endoscopic and radiographic studies, can be problematic for defining CP. It should be highlighted that CP only forms a minority of the patient population with chronic abdominal pain. In addition, morphologic changes of the pancreas that are used to diagnose fibrosis are highly non-specific for CP as they can be found in patients with diabetes, obesity, smoking, alcohol consumption and advanced age [27–30]. Further insight into the importance of opioid use in this population is gained from the long median time to opioid independence (30.1 weeks; IQR: 8.3–66.6). This is a reflection of the tolerance and sensitization seen in these patients and highlights the need for active opioid weaning post operatively.

Evaluating pain outcomes in patients with any form of chronic pain is a complex issue. However, evaluating pain outcomes in TPIAT ideally should be considered a simple issue with a simple metric, the complete resolution of abdominal pain. From the published literature on this topic it is clear that abdominal pain is common following TPIAT. Our results have demonstrated the majority of patients have complete resolution of their pre-operative abdominal pain (89%); however, many (83%) also developed a new characteristic abdominal pain following surgery that lasted more than one year in nearly half of these patients. Symptoms of gastrointestinal dysmotility, including gastroparesis, is common in patients following TPIAT and may offer a partial explanation of the development of this new characteristic abdominal pain [31,32]. This is likely further exacerbated by the development of ileus due to the dose and duration of intravenous opioid use in the perioperative? and postoperative period [33].

At present, there are limited data regarding patient selection for TPIAT. Studies in patients undergoing TPIAT and other surgical procedures to manage pain in CP have shown that the following factors are associated with poorer pain outcomes post operatively: preoperative opioid use, duration of pain, multiple endoscopic procedures, continuous pattern of pain and pancreas divisum [6,16–18]. It is intuitive that preoperative opioid use is the strongest predictor of postoperative opioid use based on the development of tolerance, dependence, and hyperalgesia which have been previously discussed. Increased duration of pain reflects ongoing nociceptive afferent into the central nervous system and resulting sensitization that may be augmented by prolonged opioid use. The number of pancreatic stents and pancreas divisum can be seen as strongly collinear variables, as pancreas divisum is commonly treated by ERCP with minor papillotomy and dorsal duct stenting. Our study did not demonstrate any association with pain outcomes and pancreas divisum or repeated ERCP. Explanations for these prior findings is that patients underwent endoscopic therapy for CP that was assumed to be due to pancreas divisum, when in fact, they may have had chronic abdominal pain with no other identifiable risk factors for pancreatitis. Pancreas divisum is the most common congenital anomaly, seen in 7–10% of the global population, and is currently implicated as a cause of ARP and/or CP only in the setting of pathogenic gene variant (s) and/or environmental factors [34,35]. The key finding in the present study, that has important implications for patient selection, is that a prior history of ARP was the only factor associated with resolution of pre-operative abdominal pain post operatively, with a trend towards significance noted for post-operative opioid independence as well (OR: 0.33, $p = 0.054$). Several studies have now shown that ARP is highly associated with the development of CP as they lie on a continuous spectrum of disease [13,36–38]. ARP was found to be the most important independent predictor of pain outcomes following TPIAT as it is the strongest predictor of CP. Importantly, morphological features of CP were not associated with pain outcomes in this study, thus patients with only morphological features of CP without a preceding history of ARP should be considered for TPIAT with extreme caution.

Preoperative central sensitization, measured by quantitative sensory testing (QST), has been shown to be associated with poorer pain outcomes in patients undergoing other pancreatic surgeries [39]. Unfortunately, this finding has never been validated in

patients undergoing TPIAT as evaluation for central sensitization is not routinely performed. Additionally, how knowledge of central sensitization ties into the surgical management of these patients remains unclear. This is an area that clearly needs to be further explored going forward in order to maximize pain outcomes from this procedure.

The strengths of the present study include a well characterized patient cohort with stringently validated episodes of AP as well as the pain outcomes. The primary limitation of the present study is the lack of quantification of central sensitization of patients prior to and after surgery. We also did not obtain quality of life assessments in our patients, but significantly improved physical and mental quality of life parameters have been shown in prior studies [40].

In conclusion, ongoing opioid use is high following TPIAT. While the majority of patients had resolution of their pre-operative abdominal pain, many develop a new characteristic abdominal pain, likely a result of persistent post-operative gastrointestinal dysmotility and/or persistent central sensitization. Finally, this data supports that ARP, the most important determinate of CP, should be considered as one of the main selection criterion for performed TPIAT. Performing TPIAT in patient with CP who do not have a history of ARP must be considered with due caution, to ensure that no patients with abdominal pain and nonspecific morphological features of CP are harmed by this morbid procedure.

## Conformation of authorship

As per the guidelines of the International Committee of Medical Journal Editors (ICMJE), we confirm that all of the listed authors have meet all of the following criteria: I) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; II) Drafting the work or revising it critically for important intellectual content; III) Final approval of the version to be published; IV) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## Disclosures

Anthony Kalloo: Equity holder for Apollo Endosurgery.

Vikesh Singh: Consultant for Abbvie, Calcimedica, and Novo Nordisk. Advisory board participant for Salix, Akcea, Nordmark, and Celltrion.

All the other authors have no disclosures.

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