



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 ≥ 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.

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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, CTSC 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 |
|---|----------------|-----------------------------------|---------------------------------------|-------|
| <i>Demographic details</i> | | | | |
| 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%) | |
| <i>Etiological factors for Pancreatitis</i> | | | | |
| 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 |
| <i>Imaging features of chronic pancreatitis</i> | | | | |
| 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 |
| <i>Preoperative clinical details</i> | | | | |
| > 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.

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