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Total Pancreatectomy with Islet Autotransplantation

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ABSTRACT

Total pancreatectomy with islet auto transplantation was developed 4 decades ago for the treatment of painful, chronic pancreatitis. This treatment is currently on the rise in both adults and children suffering from this condition. After complete removal of the pancreas, the islet cells are isolated and returned to the patient. Over time, the islets engraft into the liver and some patients are able to wean off insulin therapy. Most of the remaining patients retain c-peptide positivity indicating some level of islet function, which aids in diabetes management. Patient selection and appropriate timing of surgery is challenging due to the complexity of pain pathogenesis and variable progression of disease. Careful and comprehensive perioperative management by a multidisciplinary team is essential to optimizing patient's outcomes. This procedure is proving to have durable pain relief results in the majority of patients evidenced by improved quality of life scores and narcotic cessation after surgery. Additionally, islet engraftment has demonstrated success in the high rates of c-peptide positivity in postoperative patients and insulin-independence rates of 10-47% across studies from major centers. Ongoing research is needed in islet engraftment barriers, implantation site selection, islet imaging, and predictors of postoperative success in order to continue to advance this technology.

INTRODUCTION

Total Pancreatectomy with Islet Autotransplantation **(TPIAT)** is being increasingly utilized for the treatment of refractory pain in Chronic Pancreatitis **(CP)** or Recurrent Acute Pancreatitis **(RAP).** Total pancreatectomy was first performed in the 1940s for treatment of pancreatic tumors and later for chronic pancreatitis. Unfortunately, complete removal of the pancreas resulted in brittle insulin-dependent pancreaticogenic (type 3c) diabetes. Later, in 1977 at the University of Minnesota, total pancreatectomy with islet autotransplantation was born. Complete extirpation of the pancreas was performed to remove the inciting organ in a case of refractory chronic pancreatitis. Rather than discard the pancreas, this was processed to remove the exocrine tissue and the islet cells were then infused into the patient's portal vein in an effort to mitigate the consequences of removing the endocrine tissue during total pancreatectomy. The procedure was a success, and the patient was insulin- and pain-free for the remainder of her life [1,2]. TPIAT was later initiated at a small number of other centers in the next decade, with further development of programs in the 1990s-2000s. Current literature as of 2015 reports more than 900 patients having undergone TPIAT worldwide [3-18].

The rising employment of this procedure has propagated a parallel progression of surgical technique, islet isolation, perioperative patient care, and ongoing research. Education and awareness of chronic pancreatitis treatment among providers has led to an ongoing improvement in timing of intervention and patient selection. Perhaps most importantly, long-term analysis of TPIAT outcomes has provided information on patient selection and modifiable perioperative factors that may affect treatment success.

PATIENT SELECTION

Despite the complexity of the operative procedure, the most challenging aspect of TPIAT may be in patient selection. The goal of treatment is to alleviate pain; however, this preeminent symptom of chronic pancreatitis is incompletely understood despite numerous theories. Early on, pain was thought to correlate with morphologic changes such as ductal dilation or abnormalities leading to increases in ductal pressure and ischemia [19]. However, pain not relieved by decompression of the ductal system, pain in the setting of no significant morphologic changes, and pain levels that do not correlate with severity of fibrosis or impairment of function demonstrate that the pain of CP is multifactorial in nature [19,20].

Abdominal pain is experienced by the majority of chronic pancreatitis patients; however, there is no pathognomonic pattern that correlates with stage or extent of disease. Abdominal pain associated with nausea, vomiting, and abnormal bowel patterns can also be attributed to any number of Gastrointestinal **(GI)** complaints. Thus, thorough evaluation to rule out other culprits of pain should be undertaken, including but not limited to constipation, gastroparesis, bowel obstruction, biliary pathology, malignancy, mesenteric ischemia, peptic ulcer disease, and gastroesophageal reflux disease.

Evaluation and alleviation of reversible causes of pancreatitis should be exhausted. Maximizing medical therapy is importantprior to considering invasive management such as surgery. Therapy should optimally be aimed at the etiology rather than only symptoms, however in a subset of patients; these provide limited to no relief. Enzyme supplementation, narcotic and non-narcotic analgesics, celiac ganglion blocks, or enteral or parenteral nutrition may be utilized as appropriate. Patients with dilated ducts, a focal proximal stricture with upstream dilation, or relatively small burden of main duct stones may be amenable to endoscopic stenting, drainage,or extraction procedures for pain relief [15]. A subset of patients with tail-only or focal disease may also benefit from limited resection or surgical drainage procedures; however, care must be taken to not attempt partial resection with evidence of full organ involvement, as partial resection prior to TPIAT correlates with lower islet yields. These patients are less likely to attain insulin-independence after TPIAT as a result [14,21,22].

Another subset of patients receiving increasing recognition includes those with hereditary pancreatitis. Over the last 2 decades, over 30 mutations have been identified, with protease trypsin 1 (PRSS1) gene mutation as the first in 1996 [23-26]. Onset of symptoms generally begins much earlier in life for these patients, often before 10 years of age. Morphologic changes were found to occur at a median age of 23 years in a French study of a hereditary pancreatitis registry, along with exocrine and endocrine insufficiency in approximately one-third of patients at median ages of 29 and 38 years, respectively [26,27].Given the earlier onset of symptoms and typically diffuse involvement of the entire organ, these patients who meet criteria are given earlier consideration for TPIAT rather than partial resection or duct-drainage procedures [26]. Despite the predilection to delay major surgery for a pediatric patient, the largest cohort of pediatric patients (75 patients) demonstrated that younger children undergoing TPIAT fare better than their adolescent counterparts: 56% insulin-independence in 5-12 year-olds vs 40.5% in 13-19 year-olds. More extensive pancreatic disease equates to more severe fibrosis, which is associated with lower islet yields and lower chance of insulin independence [28]. Therefore, prolonged observation prior to surgery can have negative consequences. TPIAT has been shown to provide sustained relief from pain and improved quality of life in the majority of these children [25].

Treatment generally progresses from least to most invasive, however, many patients' disease processes are refractory to these treatments and they are subsequently on staggering doses of narcotics and subject to innumerable lost hours and days of productive life due to failure of therapy. A multidisciplinary approach is essential to identification of patients appropriate for TPIAT. Management of these complex, refractory chronic pancreatitis patients should be overseen by a group including experts in surgery, gastroenterology, endocrinology, pain management, nutrition, along with coordination of care with the patient's primary care physician. Aggressive preoperative preparation and psychological support helps patients form appropriate expectations for postoperative outcomes.

According to recent recommendations set forth by a national pancreatic workgroup, TPIAT should be considered in CP or RAP patients with intractable pain with seriously impaired quality of life due to this pain in whom medical, endoscopic, or prior surgical therapy has failed [20]. In order to aid in patient selection, the University of Minnesota has developed rigorous criteria for the diagnosis of chronic pancreatitis (Figure 1). Patients must have intractable pain for greater than 6 months with features consistent with pancreatitis coupled with a diagnosis based on imaging and abnormal pancreatic function testing. Additionally, they must have chronic narcotic dependence, impaired quality of life (may include inability to attend school or work, unable to participate in age-appropriate activities, or repeated hospitalizations), complete evaluation excluding other or reversible causes of pain, and unresponsive to previous therapies. Additionally, patients with c-peptide negative diabetes at the time of evaluation are not currently considered for islet autotransplant given the lack of benefit [14,29].

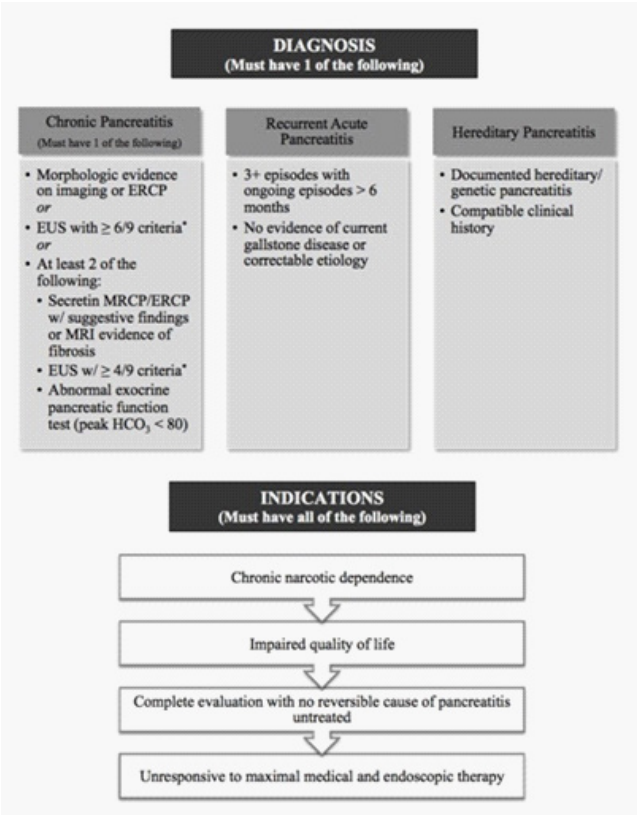

Figure 1: University of Minnesota criteria for diagnosis and indications for total pancreatectomy with islet autotransplantation (TPIAT). To be considered for TPIAT, patients must meet the criteria for diagnosis, indications for surgery, and have no contraindications. (Adapted from Bellin, et al [29]. EUS endoscopic ultrasound, MRCP magnetic resonance cholangiopancreatography, ERCP endoscopic retrograde cholangiopancreatography, MRI magnetic resonance imaging, *indicates Rosemont criteria [30]).

CONTRAINDICATIONS

TPIAT is a large, complex procedure and evaluation for the ability to undergo such an operation should occur early in the patient's assessment. Presence of severe organ disease such as end-stage pulmonary disease, cirrhosis, or severe ASHD should not undergo this operation due to high morbidity and mortality with any major operation. Illegal drug usage, active alcoholism (we require proof of abstention for a minimum of 6 months prior to operation), or poorly controlled psychiatric illness are contraindications given the poor outcomes associated with these factors. Other factors may contribute to a patient's ability to comply with the postoperative regimen and follow-up and should be closely evaluated and remedied as able. TPIAT is not currently recommended for patients with pancreatic cancer in the United States given the risk of iatrogenic spread of cancer. TPIAT for patients with Intraductal Papillary Mucinous Neoplasm **(IPMN)** is also not recommended at this time outside of clinical trials and select cases [14,20].

PREOPERATIVE TESTING

Metabolic testing prior to surgery should include fasting and postprandial blood glucose, HbA1c, glucose tolerance test, baseline and stimulated C-peptide levels. Diagnosis of diabetes is made as defined by the American Diabetes Association (fasting glucose ≥ 126 mg/dl or HgbA1c ≥ 6.5%) [31]. Islet function is evaluated with stimulatory testing: oral glucose or mixed meal testing, or intravenous glucose or arginine. A C-peptide of > 0.6 ng/mL is defined as positive [14]. Additionally, given the high rates of concomitant splenectomy with TPIAT, preoperative immunization against Meningococcus, Pneumococcus, and Hemophilus influenza are recommended.

TECHNIQUE

Common surgical approaches to TPIAT include bilateral subcostal incisions, a midline laparotomy, or an upper midline laparotomy. Alternatively, several centers have reported initiation of surgery via laparoscope or with robotic assist [32-35]. Variable degrees of adhesions are generally encountered given the chronic inflammatory process at play. Inspection of the abdomen, including running the bowel, is prudent to evaluate for occult culprits of pain or malignancy. The lesser sac is opened at this point to access the pancreas. Mobilization and extirpation of the spleen is achieved through dividing the lateral attachments and short gastric vessels, which frees up the tail of the pancreas. Splenectomy rates with TPIAT are variable across centers performing this procedure, however, it is the practice of this institution to take the spleen given the disruption of the blood supply and high incidence of early and late GI bleeding, splenomegaly, variceal formation, and infarct associated with leaving it behind [8,14,17,36].

Extensive kocherization of the duodenum allows mobilization of the pancreatic head. Next, the distal common bile duct and gastroduodenal artery may be isolated (but not yet ligated) at the

superior border of the pancreas. Although antrectomy with gastrojejunostomy is an option for reconstruction, it is the general practice of the author's institution to preserve the stomach and pylorus plus several centimeters of proximal duodenum. At the inferior margin of the pancreas, the superior mesenteric vein is identified and dissected free. Careful dissection is continued for identification of the confluence of the splenic vein and superior mesenteric vein and the superior mesenteric artery is freed at its location superior to the pancreas. The proximal jejunum is then divided approximately 10cm distal to the Ligament Of Treitz **(LOT)**, followed by division of the corresponding jejunal vessels. The LOT is opened to pass the jejunuminto the right upper quadrant.

At this point, the pancreas is only attached via the vessels, bile duct, and uncinate process. It is critical to preserve this blood supply as long as possible to minimize warm ischemia time to the islets. Thus, it is at this point that the bile duct is divided followed by division of the splenic artery, gastroduodenal artery, and splenic vein. The dissection of the uncinate process from the retroperitoneumis thencompleted. The pancreas is transferred in ice cold saline to the back table and prepared for processing by removing non-pancreatic tissue prior to being sent to the lab. It is occasionally necessary in the setting of difficult mobilization of the pancreas due to acute and chronic inflammation to resect the body and tail first. This is followed by later mobilization of head of the pancreas, with these two parts of the organ sent to the islet processing lab separately.

Reconstruction is achieved via Roux-en-Y jejunojejunostomy with each limb approximately 40cm in length. Choledochojejunostomyand duodenojejunostomy are typically performed in an end-to-side fashion. This is followed by closure of mesenteric defects and inspection to ensure appropriate orientation of reconstruction. Appendectomy and cholecystectomy may also be performed as needed at this time. Additionally, construction of a feeding jejunostomy and Stamm gastrostomy may be included at the judgement of the surgeon.These may be placed as 2 separate or a single gastrojejunostomy tube depending on the need for enteral access or prolonged gastric decompression. Of note, alternative reconstructions have been described due to prior surgery, patient anatomy, or disease process necessitating alternate resections [15].

After completion of islet isolation, the patient is heparinized (70 units/kg is the standard adult dose at the author's institution though other protocols may vary) to decrease the risk of Portal Vein Thrombosis **(PVT),**and the portal venous system is accessed with a catheter via a mesenteric vein leading to the portal system. Portal pressures are monitored closely as the islets are infused. If portal pressures become elevated to >25-30mmHg, the infusion is halted and pressures monitored, with pressures often improving and allowing completion of infusion. If portal hypertension persists, the remaining islets may be injected at an alternate site at the surgeon's judgment, most commonly the peritoneal cavity [14,26].

POSTOPERATIVE MANAGEMENT

Immediately after pancreatic resection, a continuous insulin infusion is started for the maintenance of euglycemia in an effort to prevent glucose toxicity to the engrafting islets [26,37,38]. The patient may be gradually transitioned to an outpatient regimen after enteral nutrition is established. Some patients are able to slowly transition to a diet, however, many require supplemental nutrition via gastric or jejunal feeding tube placed at the time of surgery due to poor perioperative nutrition and inability to meet caloric needs postoperatively. Exocrine supplementation should also be initiated at this time. Due to the risk of PVT, modified prophylactic anticoagulation should be started at the discretion of the surgeon in the postoperative period when bleeding risk allows. Enoxaparin at ½ mg/kg twice a day or heparin (10U/kg) at near-therapeutic doses is the practice of the author's institution [26]. To evaluate for PVT, a screening right upper quadrant ultrasound is performed at 1 week after surgery. If a PVT is identified, the patient is treated with warfarin for 3 months with follow-up ultrasound to ensure they have cleared the thrombosis.

Positive cultures of the islet isolate are frequently encountered in the postoperative period. This is attributed to instrumentation of the pancreaticobiliary system prior to TPIAT such as Endoscopic Retrograde Cholangiopancreatography **(ERCP)** or drainage procedures. A recent study at the University of Minnesota indicated this can be found in as high as 61% of islet cultures. It was demonstrated that <5% of these patients had an infectious complication caused by the same organism isolated from their pancreas or islet cell preparation. This indicates that the presence of a positive culture is generally associated with a low burden of infectious complication [39]. Of note, in the study (and the practice of the author's institution) is to initiate broad-spectrum antibiotics in the presence of positive islet cultures. These are then narrowed when sensitivities are obtained for a total of 7 days of antibiotics.

Close follow-up after TPIAT is essential due to the complexity of pain management, drain removal, metabolic testing, glucose control, enzyme replacement therapy, imaging changes, nutrition, polypharmacy, and monitoring for complications. The recommendations from a gathering of experts in chronic pancreatitis at the 2014 Pancreasfest include lifelong monitoring for diabetes at least annually, life-long pancreatic enzyme therapy, and nutritional monitoring for steatorrhea, weight maintenance, and fat-soluble vitamin levels on at least an annual basis [20]. Careful observation for attrition of islet cells is important, as patients may require eventual initiation of insulin even after obtaining insulin-independence for a number of years. Avoidance of corticosteroids is also important to avoid harm to the islets, which should be communicated to patients' PCPs, particularly when traveling from an area lacking familiarity with TPIAT [40]. Additional education should include potential for changes seen on postoperative imaging. Islet engraftment into the hepatic sinusoids, blockage of terminal portal vein branches, and local insulin release may result in hepatic structural changes [41]. This has been associated with an increase in echogenicity on ultrasound and nodular appearance on ultrasound and Magnetic Resonance Imaging **(MRI)** [41,42].

OUTCOMES

With over 900 TPIATs reported in literature to date, more than half of those have been performed at the University of Minnesota, which includes approximately 600 patients [14,15]. Additional major centers reporting their experiences include Leicester, University of Cincinnati, University of Arizona, University of Alabama, Medical University of South Carolina, Digestive Disease Institute Cleveland, and Baylor Research Institute among others [8,18,9,7,13,17,16]. Though TPIAT is not currently recommended for benign or malignant tumors within the United States, a small number of centers in Italy [5,6], Korea [10-12], and Geneva [43] have expanded their indications to include this subset of patients.

In the largest published series with comprehensive data of TPIAT for CP, patients with mean ages 35 - 44 have undergone surgery after suffering symptoms of pancreatitis for a range of 5.4 to 9.2 years [8,14,16]. The most frequentlyreported etiology of patients undergoing TPIAT is idiopathic, followed by alcoholic pancreatitis. Complexity of patient selection is highlighted by the fact that a range of 12-80% of patients reported in these series have undergone prior pancreatic resections before TPIAT. This has been shown in multiple studies (particularly a lateral pancreaticojejunostomy or distal pancreatectomy) to have detrimental effects on islet cell harvest, and thus success of the transplanted beta cell mass [14,22,44].

Pain outcomes are important but difficult to assess. Patients are often on large doses of narcotics for extended periods of time which can have previously unforeseen consequences (cite Moran pancreatitis pain study and study from GI perspectives paper)or have concomitant but unrelated causes for pain, thus complete cessation of narcotics is often not the best indicator of treatment success. This is currently one of the more common ways pain outcomes are reported at this time. Despite these complicating factors to narcotic weaning, these major centers have demonstrated that TPIAT can successfully alleviate pain in the majority of CP patients [7-9,13-18]. Studies show rates of narcotic independence at 1 year after surgery range from 55%-71% [8,9,14,18]. There is additional improvement over time likely due to the effect of tapering long-term narcotic users and aggressive postoperative therapy. Pain scores also improved after surgery when compared to their preoperative state.

Though results are variable and most show some degree of islet attrition over time, the cumulative experience of major centers show that islet auto transplantation does attenuate the otherwise complete insulin deficiency associated with total pancreatectomy. Insulin independence rates range from 10% to 47% across studies [7-9,13-18]. There is also a subset of patients who retain C peptide positivity (indicating partial islet function) and gain a benefit by ameliorating the potentially severe glycemic swings seen in pancreatogenic diabetes, thus improving diabetes management [37]. These rates were reported to be as high as 90% and 100% at the University of Minnesota and Leicester centers respectively, demonstrating successful islet engraftment [8,14]. Many patients who do end up requiring insulin after surgery still find surgery to be ofbenefit, withstudies showing that postoperative insulin use did not negatively impact quality of life scores [45].

Despite this evidence of successful beta-cell function after islet auto transplantation, recent studies have brought to light the uncertain status of the other endocrine cells native to the pancreas. Early observations in the 1990s suggested that intrahepatically infused islets had absent glucagon responses to hypoglycemia [46]. This was made more evident by a recent study showing that patients with both intrahepatic alone islets had virtually absent glucagon responses to hypoglycemia, while those with both intrahepatic and extrahepatic infusion of islets demonstrated a response to similar to controls [47]. Further research is necessary in this arena to maximize our understanding of post transplantation physiology and the benefit of TPIAT for chronic pancreatitis patients.

CONCLUSION

TPIAT is a safe and effective treatment strategy for this complex and frustrating disease process after almost 4 decades of experience. Ongoing research is improving our ability to select patients for TPIAT and optimize timing of intervention, though there is a significant room to improve our understanding of the pathogenesis of chronic pancreatitis pain and thus tailor therapies appropriately. Ongoing research in islet processing, preoperative patient assessment and selection, islet engraftment barriers, and islet implantation sites will likely contribute to refining postoperative endocrine function, pain relief, and quality of life for patients in the future.

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