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Total Pancreatectomy and Islet Auto-Transplantation for Chronic Painful Pancreatitis: An Overview

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Abstract

Chronic pancreatitis is a progressive and irreversible process that can lead to pain, pancreatic dysfunction, and even malignancy. Management can be difficult, with some patients proving refractory to standard medical or endoscopic treatments. These patients generally depend on narcotics to manage their symptoms. Total pancreatectomy and Islet Auto-Transplantation (TP-IAT) can offer relief for such patients by removing the root cause of their pain. The pancreas is entirely resected and islets are isolated then infused back into the patient. The islets are most commonly infused into the liver, where they engraft and begin to function within months. Pain relief is substantial and patients report improved quality of life following the procedure. Approximately one third of patients achieve insulin independence (19-40% of cases, variable by institution). Most of the patients who do go on to require insulin demonstrate some degree of islet function, thus minimizing the severity of their diabetes and associated complications. TP-IAT is an effective treatment for patients with debilitating chronic pancreatitis that can offer pain relief, narcotic independence, and improved quality of life to recipients.

Keywords

Chronic Pancreatitis, Pancreatectomy, Islet transplantation, autologous, TP-IAT, Review, Outcomes

Introduction

Chronic pancreatitis (CP) is an often painful and debilitating disorder that remains a challenge to both patients and physicians. It is a rare disorder, with an estimated incidence of 0.2% to 0.6% in the United States [1,2]. Despite its rarity, the economic impact of CP is substantial, with total estimated annual health care expenditures of $2.6 billion [3]. Frequent hospital admissions, emergency department visits, and lost days of work become a tiresome and expensive way of life for patients with recurrent or constant pain due to CP. Additionally, if left untreated, many patients will develop exocrine and endocrine insufficiency and some will go on to develop pancreatic cancer [4,5].

The goal of treating CP is to reduce pain and restore quality of life. Initial interventions are aimed at correcting the mechanical, metabolic, immunologic, or pharmacologic causes of the disease. Medical options can include narcotic analgesics, pancreatic enzymes (which both reduce pancreatic stimulation and treat pancreatic exocrine insufficiency), and nerve block procedures [6,7]. Endoscopic interventions may include stone extraction, sphincterotomy, stricture dilation, or stent placement [6,8]. If medical or endoscopic treatments are not successful, patients may be candidates for surgery.

Surgical techniques include partial pancreatic resection (Whipple or distal pancreatectomy) and drainage procedures such as lateral pancreaticojejunostomy (Puestow) or variants (Frey, Beger). Patients often have transient pain relief, but due to the diffuse and progressive nature of CP, pain eventually recurs in up to 50% of patients [9,10]. Furthermore, patients frequently continue to develop exocrine and endocrine insufficiency despite surgery [11-14].

A total pancreatectomy (TP) completely removes the root cause of pancreatitis pain. The diseased gland is excised completely and, unlike with partial resections or surgical drainage procedures, there is no potential for pancreatic duct leakage [15]. Performed in isolation, without preservation of any beta-cell function, a TP would result in brittle surgically-induced diabetes with the added problem of exocrine pancreatic insufficiency. However, when combined with an intraportal islet autotransplant (TP-IAT), beta-cell mass can be preserved following TP allowing for insulin secretory capacity and reduction of diabetic symptoms and complications.

The world's first TP-IAT was performed at the University of Minnesota in 1977 to treat a patient with painful CP [16]. She was remained pain-free and insulin-independent 6 years later, when she died of unrelated causes [17]. Since that time, outcomes following TP-IAT have been generally favorable, with the vast majority of patients reporting improved pain and quality of life and many patients requiring little to no insulin to manage post-operative diabetes. With these favorable outcomes, the procedure has gained increasing acceptance as a treatment for CP. Presently, there are over

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20 centers worldwide with active TP-IAT programs and over 1,000 of these procedures have been reported in the literature [18-30].

Screening Candidates

Due to the extensive nature of the operation and the potential complications of insulin dependence, gastrointestinal dysmotility, and post-splenectomy infection, patients must be selected with considerable care. Criteria for selection of patients for TP-IAT have evolved over time. Generally, the patient must meet diagnostic criteria for chronic or acute relapsing pancreatitis, have pain that is consistent with pancreatitis despite previous medical and/or endoscopic procedures, and demonstrate significant impairment in quality of life resulting from pain. The decision to offer a TP-IAT is made by a multidisciplinary team consisting of gastroenterologists, surgeons, endocrinologists, pain specialists, health psychologists, dietitians, and nurse coordinators. All patients and families must receive information on the use of pancreatic enzyme supplementation, the risk of insulin-dependent diabetes, the risk of post-splenectomy infection, the likelihood of long-term pain relief, and any other available therapeutic options. Patients also undergo psychological and pain evaluations. Those discovered to have complex substance abuse issues or difficult pain management regimens may be offered additional approaches for anxiety, chemical dependency, and pain management prior to consideration of TP-IAT.

TP-IAT should not be offered to patients with active alcoholism or illegal drug usage, poorly controlled psychiatric illness, or anticipated inability to comply with the complicated postoperative regimen [31]. Additionally, patients with pancreatic malignancy, cirrhosis, portal vein thrombosis, portal hypertension, high-risk cardiopulmonary disease, or C-peptide negative diabetes are not considered eligible for the procedure [30,31]. TP-IAT has been performed in the presence of benign pancreatic tumors by some centers [32-35].

Chronic pancreatitis has been shown increase patients' risk of pancreatic adenocarcinoma; approximately 5% of patients with CP will develop carcinoma over a period of 20 years [36]. The risk is even greater in patients with hereditary pancreatitis, whose risk approaches 40-55% in the same time period [37]. Currently, no formal guidelines exist for screening potential TP-IAT patients for pancreatic adenocarcinoma. Certainly, these patients undergo extensive imaging during the course of their disease pre-TP-IAT. If radiographically-suspicious lesions are identified on imaging, the possibility of malignancy should be investigated, noting that serological biomarkers are minimally helpful in distinguishing early cancer from chronic pancreatitis [38].

There is a theoretical risk that patients after TP-IAT could develop pancreatic cancer in transplanted cells within the liver. Investigators in Minnesota have reported that they have not seen any cancer in the liver in a cohort of 484 patients with 2,936 person years of follow up [39]. This does not, however, rule out the possibility.

Surgical Procedure

The surgical technique for TP-IAT has evolved over the decades and had been described in detail elsewhere [30,40]. Briefly, the pancreas is removed along with the C-loop of the duodenum and distal bile duct, followed by gastrointestinal reconstruction. A duodenum-preserving operation has been described, but has been associated with duodenal ischemia and thus has fallen out of favor [17,26,41]. A cholecystectomy is routinely performed and an appendectomy is often included in the procedure if not previously performed.

The decision to perform a splenectomy is institution, surgeon, and patient-dependent [23,41,42]. Spleen-sparing total pancreatectomy is feasible in many cases and allows patients to avoid potential post-splenectomy infections [30,41]. However, spleen preservation may be technically difficult due to severe fibrosis, calcification, pseudocyst, or hemorrhage [41]. Additionally, spleen preservation carries the risk of splenic congestion with gastric varices, ischemia, infarction, intrasplenic collections, and portal vein thrombosis, all of which may require reoperation [41,42].

Gastrointestinal reconstruction is completed while the pancreas is processed in the islet laboratory. This can be accomplished with a choledochojejunostomy along with either a duodenostomy or duodenojejunostomy. Duodenojejunostomy with roux-en-y configuration is preferred by some surgeons in order to avoid the complication of bile reflux [40]. A gastrojejunostomy feeding tube is routinely placed to allow for post-operative gastric decompression and jejunal tube feeding.

The critical element of the procedure is the preservation of blood supply to the pancreas until just before its removal. This decreases warm ischemia time and maximizes islet preservation. Following resection, the pancreas is immediately placed in cold balanced electrolyte solution for transport to the islet laboratory. Recently, TP-IAT has been performed in minimally invasive fashion [43-46].

Islet isolation and infusion

The basic method of islet isolation has remained the same with minor modifications throughout the years. The process involves dispersion of the pancreas in a series of steps, which are variable across institutions. First, a collagenase solution is injected into the main duct to distend the pancreas and enzymatically disrupt the exocrine pancreas (sparing the islets) [47]. Next, digestion in a shaking (Ricordi) chamber is performed at 34° to 37° C to mechanically disperse the pancreatic tissues [48].

After digestion, the islets are generally infused as an unpurified preparation in order to retain the greatest number of islets possible. Purification is reserved for select cases when a large volume of pancreatic digest (≥ 0.25 ml/kg patient body weight) is obtained [49-51]. The final islet tissue preparation is suspended in culture medium with human serum albumin, buffering solution, antibiotic, and heparin to protect against aggregation before infusion.

Heparin is administered prior to islet infusion, most commonly with an initial bolus of 70 units/kg body weight [50]. Islets are infused into the portal system over a period of 30 to 60 minutes, typically through a cannula inserted into the splenic vein stump. Portal pressures are monitored and the infusion is stopped if any of the following criteria are met: the total tissue volume exceeds 0.25 ml/kg, the intraportal pressure exceeds 25 cm H_2O, or the portal blood flow decreases to less than 100 ml/min flow when measured by an electromagnetic flow meter. Any remaining islets are then implanted in an alternate site, such as intraperitoneal, beneath the renal capsule, or the sub-mucosal layer of the stomach [52]. No matter the site, the islets initially survive by nutrient diffusion until neovascularization occurs [53,54]. During this time, the islets are minimally functional and are susceptible to environmental stress [42].

Early postoperative care

After islet infusion, patients are placed on a heparin drip or low-molecular-weight heparin to minimize the risk of portal vein thrombosis. Portal vein thrombosis remains a risk in the days following islet infusion [55]. As such, surveillance by Doppler ultrasound has been recommended during the immediate postoperative period. If discovered to have a portal vein thrombus, the patient is prescribed a 3-month course of warfarin [56].

Patients are routinely given intravenous narcotic analgesics in the period immediately following TP-IAT. Notably, use of a dexmedetomidine infusion and paravertebral nerve blocks can augment early postoperative pain control and reduce narcotic analgesia needs [57-60]. After conversion to oral analgesics, patients are weaned off these medications gradually, most often in the outpatient setting in collaboration with their local providers.

Return of gastrointestinal motility and function is often delayed postoperatively. With a gastrostomy tube in place, symptomatic relief from gastroparesis can be accomplished by venting. Enteral feeds are initiated early postoperatively. Pancreatic enzymes are added to the tube feed formula to compensate for the patient's complete

exocrine insufficiency. As delayed gastric emptying improves, oral diet is reintroduced and tube feed volume is reduced. All patients are educated on use of pancreatic enzymes, starting with 1,000 lipase units/kg/meal and advancing to a goal dose of 1,500. Fat-soluble vitamin supplementation is recommended and serum vitamin levels are monitored for life [61].

Autotransplanted islets are not capable of full function immediately following infusion. During recovery and engraftment, tight glucose control is necessary to protect against beta-cell functional stress [62]. As such, patients are started on an insulin infusion immediately following TP-IAT. Once a stable tube-feeding regimen is established, patients are transitioned to subcutaneous insulin. Use of exogenous insulin continues for at least 3 months while engraftment of the islets takes place. Thereafter, insulin can be weaned if blood glucose levels remain in a near-normal target range, indicated by a fasting blood glucose of < 125 mg/dl, postprandial glucose < 180 mg/dl, and glycated hemoglobin of ≤ 6.5% [30]. Outside of those ranges, patients must be maintained on insulin.

Patients are followed up multiple times in the first year after TP-IAT. Labs and follow-up appointments are recommended at 3 months, 6 months, 1 year, and then annually. Laboratory studies at these intervals include fasting glucose and C-peptide, stimulated glucose and C-peptide, and hemoglobin A_{1c} level.

It has become routine at the author's institution to distribute quality of life surveys to patients undergoing TP-IAT before surgery and again at 3 months, 6 months, 1 year, and then annually [63]. The surveys include the RAND Medical Outcomes Study 36-item Short Form (SF-36) health survey as well as additional questions about narcotic use, pain symptoms, "pancreatic pain" (whether or not it was similar to preoperative levels), and insulin requirements [63].

Surgical complications

The in-hospital mortality following TP-IAT has been reported as 0-2% [23-26,30,64]. Surgical complications requiring reoperation under general anesthesia have been reported at a rate of 4.4-15.9% of patients [26,30,64-67]. These complications include bleeding, anastomotic leaks (both biliary and enteric), intraabdominal abscess, bowel obstruction or ischemia, wounds requiring debridement, and splenic bleeding or ischemia in patients with spleen-preserving TP-IAT [26,30]. A subset analysis of patients with post-operative bleeding revealed that patients with post-infusion portal pressures > 25 cm H_20 have a higher risk of post-operative bleeding (15% vs. 7.4%) [30].

A recent study using National Surgical Quality Improvement Program (NSQIP) data compared TP-IAT vs. TP alone and noted that the IAT is associated with greater risk of major perioperative morbidity (41% vs. 28%) and blood transfusion (20% vs. 7%) as well as a longer hospital stay (13 days vs. 10 days) [68]. There was no difference in mortality or minor morbidity. Notably, this study did not include any follow-up data after discharge and could not make comment on long-term outcomes related to glycemic control. While the short-term morbidity appears to be higher in TP-IAT patients than TP patients, this must be weighed against the morbidity of inevitable pancreaticogenic diabetes resulting from TP alone.

Islet function

Islet function after TP-IAT is variable among patients. Patients are classified as either 1. Insulin-independent, 2. Partial graft function (stimulated C-peptide ≥ 0.6 ng/dl or, if C-peptide unknown, the ability to maintain target glucose levels using only long-acting insulin or with only rare short-acting insulin), or 3. Insulin-dependent (stimulated C-peptide < 0.6 ng/dl or need for daily short-acting insulin) [30]. The most important predictor of insulin independence is islet yield at the time of operation [30]. Islet yield is negatively affected by prolonged duration of disease, previous pancreas surgery (especially lateral pancreaticojejunostomy), and alcoholic etiology [22,25,28,31,69,70].

Overall, patients achieve insulin independence at a rate of 19-40% at 1 year [23,24,30,66,71]. Of patients with yields of > 5000 IEQ/kg, greater than 70 % are insulin independent at 3 years, highlighting the importance of maximizing islet yeilds [30]. Those who attain insulin independence must continue to be monitored for diabetes since attrition over time has been reported by multiple institutions [23,30].

Importantly, the majority of patients who undergo TP-IAT demonstrate some degree of islet function, thus minimizing the severity of their diabetes and associated complications. In the Minnesota series, 49% of patients had partial graft function at 1 year based on the criteria listed above, meaning only 23% were considered insulin dependent [30]. Several other institutions classify islet function based on daily insulin requirements. For instance, in a recent Cincinnati series, 38% of patients required fewer than 20 units daily and were thus classified as partial graft function [23]. In a series from Leicaster comparing TP-IAT to total pancreatectomy alone, the group receiving islets had a significantly lower daily insulin requirement at 22 IU compared with 35 IU [72].

Once successfully engrafted, autotransplanted islets appear to function similar to native islets. Dynamic assessments of β- and α-cell secretion stimulated by intravenous arginine and glucose show that both intrahepatic cell types function normally in terms of magnitude and timing of secretion [73]. More robust insulin secretion is seen in patients with higher islet mass transplanted.

Quality of life

The Rand Corporation SF-36 is a survey which measures Health Related Quality of Life (HRQOL) and has been used at multiple institutions to assess patients before and after TP-IAT [23-25,30,74,75]. Overall, before TP-IAT, patients show below-average HRQOL scores compared with the standardized US population, with mean Physical Component Scale (PCS) and Mental Component Scale (MCS) scores at 2 and 1.5 standard deviations lower than average [30,67]. After surgery, scale scores for all 8 of SF-36 health dimensions, including PCS and MCS, have been repeatedly shown to improve [23,25,30,75]. Additionally, 85-91% of patients report overall improvement in their health at 1 year after TP-IAT [23,30]. These results have been shown durability; SF-36 surveys at 5 years and beyond (range 60-132 months) demonstrate persistent improvements in all subscales from baseline values [23]. Importantly, patients with daily insulin requirements also show significant improvements in HRQOL, though the degree of improvement in this group has been variable across institutions [30,74].

Pain resolution

Patients undergo TP-IAT to alleviate pain, which makes post-operative pain control a critical outcome to assess. Prior to undergoing TP-IAT, most patients have been on narcotics for several years, with a mean duration of 3.6 years [30]. In the Minnesota series, daily or intermittent narcotic use decreased from 100% of 207 patients pre-operatively to 91, 61, 54 and 51% of patients over 3, 6, 12 and 24 months post-operatively [30]. Similar results have been reported from other institutions. Cincinnati reports 55% narcotic independence at 1 year, with improvement to 73% independence at 5 years [23]. Arizona has reported that 71% of patients are "pain-free" and off narcotics at 1 year [24]. Regardless of narcotic use, 94% of patients in the Minnesota study stated their pain had improved at 1 year [30].

Those who continue to report pain following pancreatectomy present a perplexing issue since the original source of their pain has been removed. It has been postulated that such pain stems from irreversible maladaptive central pain pathways that develop over the duration of CP [67,76]. Postoperative gastrointestinal motility disorders may play a role as well [77].

Conclusion

Total pancreatectomy with islet autologous transplantation is an effective treatment for patients with debilitating chronic pancreatitis that is refractory to other treatments. Utilization of TP-IAT in the treatment of CP has steadily increased over the past 3 decades and

can offer pain relief, narcotic independence, and improved quality of life to recipients. TP-IAT preserves some degree of islet function in the majority of patients, minimizing the burden of surgical diabetes. Additionally, TP-IAT has also been shown to be an effective cost-saving strategy over more conservative measures in patients with severe CP [64]. While these successes are encouraging, TP-IAT continues to present significant implications of long-term diabetes, pancreatic exocrine insufficiency, potential surgical complications, and occasional difficulty with narcotic weaning. Careful patient selection remains paramount.

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