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Review Article

Clinical and Medical Engineering in Chronic Pancreatitis: Total Pancreatectomy with Islet Autotransplantation (Tpiat)

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Abstract

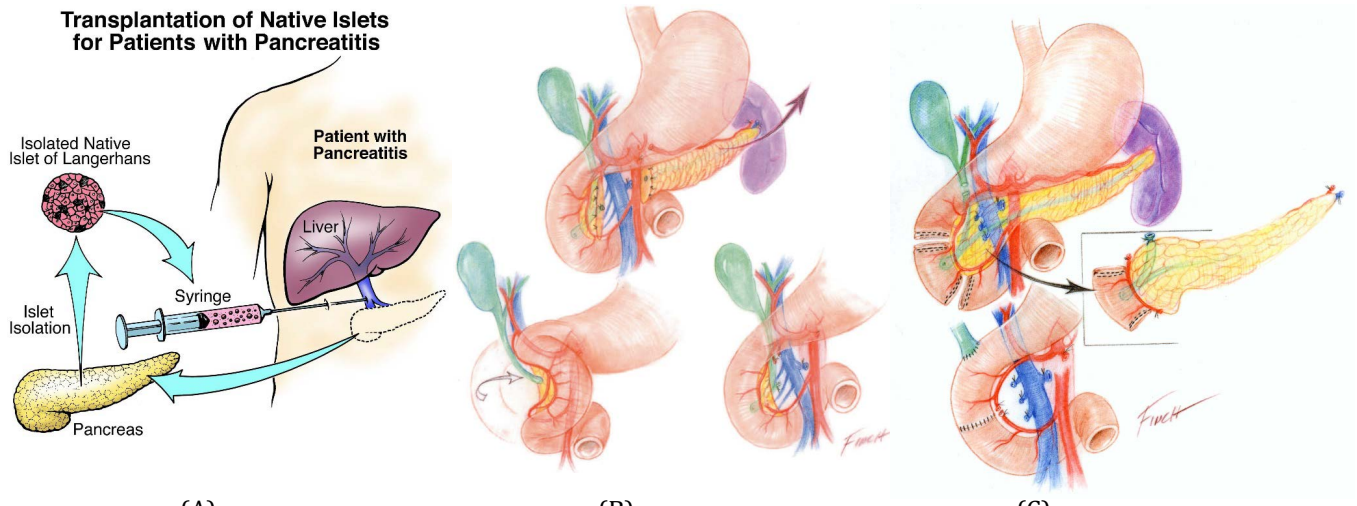
The first successful total pancreatectomy with islet autotransplant (TPIAT) for the treatment of chronic pancreatitis was performed in 1977. Since then, the procedure continues to gain widespread acceptance as a reliable and effective treatment option to (1) improve or cure the associated chronic pain syndrome; (2) prevent the development of brittle type 3c diabetes mellitus by alleviating hypoglycemic complications associated with total pancreatectomy; (3) and prevent the potential development of pancreatic cancer in this high-risk population. TPIAT is a complex procedure with a wide range of potential complications that are intrinsic to its two components: total pancreatectomy (TP) and islet autotransplantation (IAT). Mounting evidence in the literature supports TPIAT as an approach that can be done safely at experienced centers using open, laparoscopic, and/or robotic techniques with little morbidity and mortality. From the surgical perspective, the procedure is standardized and can be safely performed in adult and pediatric patients with debilitating chronic pancreatitis. Islet yield and function determine metabolic outcomes.

Keywords: Tpiat, Islet Autotransplant, Chronic Pancreatitis, Total Pancreatectomy, Completion Pancreatectomy, Robotic Pancreatectomy, Sling Maneuver, Real-Time Doppler Ultrasonography.

Introduction

Autografts of any kind are essentially living donor transplants, even though the recipient is the source of the tissue [1]. Islet autografts, to prevent or minimize post-pancreatectomy diabetes, have their allograft counterparts, to cure de novo diabetes, in living donor segmental pancreas transplants and in living donor islet allografts. Islet allotransplantation has evolved from an experimental to an increasingly established procedure over the past 2 decades in part because of the early success seen with islet autotransplants. The concept of islet allotransplantation began in 1893 when Dr. P. Watson Williams grafted three fragments of a sheep pancreas into a 15-year-old boy with diabetic ketoacidosis. There was an immediate and temporary improvement in glycosuria, however, the implants were rejected and the boy died 3 days later [2-4]. In 1916, pancreatic fragments from a cadaver were transplanted into a patient with type 1 diabetes [2, 4]. These early attempts paved the way for further efforts to transplant pancreatic tissues in diabetic patients. In the 1960s–1980s, islet isolation techniques were developed and refined with the introduction of intraductal digestion using collagenase and purification via density gradient [5-7]. All of these initial attempts were aimed at curing type 1 diabetes mellitus through islet allotransplantation. Graft outcomes were initially dismal due to immunological and immunosuppressive challenges and the field evolved from islet allotransplantation to islet autotransplantation (IAT). With a different and novel indication identified, greater success was achieved.

On February 14, 1977, Drs. John Najarian and David Sutherland performed the first human islet autotransplant in a patient with severe chronic pancreatitis at the University of Minnesota [8, 9]. As mentioned earlier, the islet autograft was considered a living donor transplant, even though the recipient was the source of the tissue. Consequently, this first autograft was followed just a short time later by the first living donor islet and pancreas allotransplants in type 1 diabetics. The objective of islet autotransplantation has not changed in the decades since: to alleviate the patient from pain and prevent the development of brittle diabetes. A near total pancreatectomy (TP) (> 95%) was performed, leaving only a small rim of duodenum with an intact common bile duct behind [Fig. 1]. The islets were crudely isolated by chopping the pancreatic tissue and employing collagenase for digestion. The patient was insulin independent for 6 years, until her death which was unrelated to the IAT [8-10]. This was the first time that insulin independence was achieved long-term after any type of an islet transplant.



(A) (B) (C)

Figure 1: Schematic Drawing Of (A) The Principles Of Tpiat And (B, C) Surgical Technique As Described By Sutherland Et Al.

At the time of this writing (January 2022), islet allotransplantation for the treatment of type 1 diabetes mellitus is still not a routinely performed procedure and outcomes trail those of whole organ pancreas transplants [11-14]. In addition, islet allotransplantation in the United States is unfortunately not reimbursed by the Centers for Medicare and Medicaid Services (CMS) and by most private insurance companies. In contrast, total pancreatectomy with islet autotransplant (TPIAT) is a highly successful procedure in patients with chronic pancreatitis (CP) and intact endocrine function. Thus, in the United States, the procedure is covered by many private insurance companies.

CP is a progressive and irreversible disease that eventually results in complete exocrine and endocrine pancreatic insufficiency, insulin-dependent and brittle diabetes mellitus, poor quality of life (QOL), debilitating pain, and nutritional deficits. Patients are often subject to numerous procedures in an effort to control pain, become dependent on narcotics, and often require parenteral nutrition. CP accounts for more than 125,000 outpatient visits and 25,000 hospitalizations yearly [15].

Most of the patients are medically managed initially analgesics like opioids, pregabalin, and acetaminophen; pancreatic enzyme replacement therapy, nutritional management, antioxidant management are the main pillars of conservative medical management [16-18]. Use of other less conventional modalities such as ketamine and somatostatin analogues has also been described. Advanced endoscopic therapies with use of various stents and extracorporeal shock wave lithotripsy (ESWL) are more frequently used than ever in these patients to help with ductal issues like stricture and stones rather than dealing with parenchymal pathology.

Celiac plexus blocks and splanchnic nerve ablation are considered when these treatment fails. New nonsurgical modalities such as radiotherapy, which can have anti-inflammatory and analgesic effects have been suggested, but further research is warranted [19, 20].

When medical and endoscopic management fails, surgery may be an appropriate next step. However, the choice of surgery is controversial [16-18]. Historically, the Whipple procedure was considered a more reasonable treatment option for patients with CP than total pancreatectomy (TP), also owing to the concept that the pancreas head is the pacemaker of the disease. In general, surgical procedures have evolved overtime for CP and can be classified as (a) resections, (b) drainage procedures, and (c) a combination thereof. Due to mostly unsatisfactory outcomes of head or tail resection and various drainage procedures (e.g., Puestow, Duval), more complex, refined procedures such as the duodenum-preserving pancreatic head resection as well as the Frey and Beger procedures have been introduced although the Beger and Frey procedures (and their subsequent modifications by others) have demonstrated similar efficacy compared to the Whipple operation, there remains a subgroup of patients that continue to have recalcitrant pain after these partial resections [21-24]. Drainage procedures and partial resections mostly fail long-term because of ongoing or recurrent chronic pain syndrome as these procedures leave diseased tissue behind [17, 18].

When partial pancreatectomies and drainage procedures fail to control pain, completion pancreatectomy is the logical next step, but many surgeons are reluctant to perform this procedure. Complete removal of the pancreas—either as total or completion pancreatectomy—is considered by many a last resort because of the development of a very brittle form of insulin-dependent diabetes mellitus that is frequently associated with recurrent hypoglycemic episodes and hypoglycemic unawareness. The annual mortality risk of hypoglycemic unawareness has been estimated to range between 2% and 8% [25].

Of note, between 2002 and 2013, 1006 TPs and 825 TPIATs were performed (with similar costs) in the United States in patients with a diagnosis of chronic pancreatitis, but only combined with an islet autotransplant (IAT), TP becomes arguably the best treatment option to alleviate pain, pre-

vent the development of brittle diabetes and hypoglycemic unawareness, and eliminate the risk of pancreatic cancer in the absence of any remaining pancreatic tissue [26]. For the last two decades, it has been shown that total pancreatectomy with islet autotransplant (TPIAT) is a safe and effective therapy for the management of CP. In fact, a large series of 742 patients observed that TPIAT produces durable pain relief and sustained islet graft function even past 10 years postoperatively and contributed to the procedure's gaining popularity [27, 28].

Indications and Contraindications

Indications: Diffuse disease in all parts of the pancreatic parenchyma is the main indication for TPIAT. These patients typically suffer from severe chronic pain syndrome, depend on narcotics or other analgesics for at least six months, failed various types of medical and endoscopic therapies and have an extremely poor quality of life (QOL).

Other candidates for TPIAT are patients with recurrent acute pancreatitis and diffuse fibrosis who require 3 or more hospital admissions per year. This includes a variety of etiologies such as pancreatic ductal anomaly or genetic mutations like cationic trypsinogen (PRSS1), transmembrane conductance regular (CFTR), and serine protease inhibitor Kazal type 1 (SPINK1) mutations. Pediatric patients with similar pathologies and inability to maintain weight or learning disabilities are also considered for TPIAT.

Rarely is TPIAT performed in patients with intraductal papillary mucinous neoplasm (IPMN), pancreatic adenocarcinoma, trauma or uncommon diseases such as pancreatic cystosis in patients with cystic fibrosis [Fig. 2]. One study reported that recurrence rates and metastatic disease are relatively low in selected cancer patients undergoing TPIAT [29]. In that series of 31 patients with malignant disease who underwent TPIAT, three developed liver metastases [28]. IAT has also been performed in patients with traumatic injury [30-32]. In a small series, patients with partial pancreatectomy after trauma were autotransplanted (41–82 h later) with their own islets [32]. In contrast to CP, the evidence-based use of TPIAT in neoplasms and trauma is very limited.

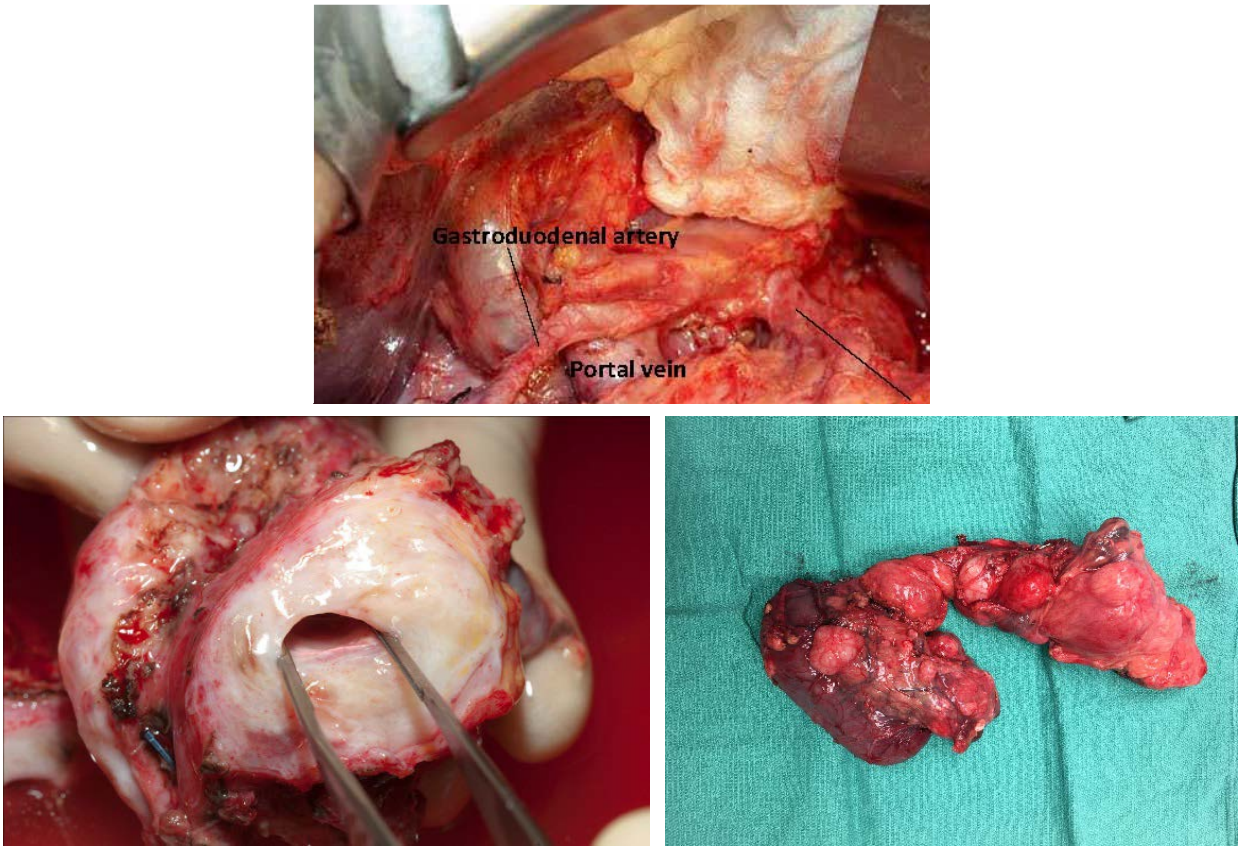


Figure 2: (top) Anterior Surface of Pancreas during Total Pancreatectomy. (Bottom left) Dilated Pancreatic Duct in Patient with Severe Chronic Pancreatitis. (Bottom right) top for cystic fibrosis.

In general, patients who are considered for TPIAT should have adequate glycemic control as indicated by normal hemoglobin A1C, fasting and stimulated c-peptide, glucose tolerance test and/or continuous glucose monitoring. Pre-diabetic patients who demonstrate good insulin secretion as indicated by stimulated c-peptide tests are also considered as candidates with the understanding that the procedure is primarily done for improvement of pain and QOL. These patients will certainly require some insulin administration but will not develop brittle diabetes. IAT should still be attempted in pre-diabetic patients as even a low islet yield can prevent the development of brittle diabetes with wide plasma glucose fluctuations, hypoglycemic episodes and hypoglycemic episodes. In addition, patients should demonstrate the capability and willingness to regularly monitor their glucose metabolism post-operatively, be able to administer insulin

(if necessary), adhere to nutritional recommendations, and be motivated for postoperative weaning of pain medications.

Contraindications

Patients unable or unwilling to adhere to complex medical management and/or comply with close follow-up monitoring including weaning of pain medication(s) should not be considered candidates for TPIAT. Preexisting liver disease and portal vein thrombosis are usually exclusion criteria if the liver is the site of islet infusion and engraftment. Patients with a hypercoagulable disorder are not an absolute contraindication but should certainly be very well selected [33]. Age (< 6 or > 70 years) is not a contraindication.

Patients with ongoing alcohol abuse should be excluded. Patients with alcoholic pancreatitis who have not gone through, or are not willing to participate in, alcohol abstinence programs continue to have poor long-term QOL and no improvement in pain scores [4]. It has been shown that patients with chronic alcohol-induced pancreatitis are also less likely to have a successful islet isolation [34]. Likewise, patients with active substance abuse and psychiatric illness should be excluded. Patients on high doses of narcotics for intractable pain have to be involved in a pain management program and/or regularly see a pain specialist before surgery. A poor support network is a relative contraindication.

Patients with multiple comorbid conditions should only be considered after thorough cardio-pulmonary work up. The incidence of non-alcoholic steatohepatitis (NASH) is rising and some patients do have fatty liver detected on pre-operative investigations. Liver histopathology can influence the outcome of surgery and hence severe fatty liver disease in CP patients is a relative contraindication [35, 36]. This is an important consideration specifically in the context of the frequent development of atypical steatosis after TPIAT, implying that the procedure itself is the causal factor [37]. Insulin-dependent diabetes mellitus and/or low C-peptide levels are considered (relative) contraindications to islet autotransplant.

A consensus of a consortium of experts discussing indications and contraindications for TPIAT was published in 2014 and is summarized in Table 1. As the field of TPIAT continues to evolve, the current recommendations are still debated among specialists. To date, the available evidence is primarily limited to center-specific experiences and, thus, limited validity of recommendations [38]. In 2017, the first multi-center, prospective, observational cohort study of patients undergoing TPIAT was launched to provide comprehensive and inclusive information on all aspects of TPIAT [39].

Table 1: Excerpted Recommendations from PancreasFest on TPIAT [33]. Adapted from Bellin et al.

Statement	Evidence level	Grade
Guidance Statement 1 The primary indication for TPIAT is to treat intractable pain in patients with impaired quality of life due to CP or RAP in whom medical, endoscopic, or prior surgical therapy have failed.	2A	B
Guidance Statement 2.1 TPIAT should not be performed in patients with active alcoholism, active illicit substance use, or untreated/ uncontrolled psychiatric illness that could be expected to impair the patient's ability to adhere to complicated medical management (pain medication taper, pancreatic enzyme therapy, diabetes cares, and frequent clinic follow up). Patients with poor support networks have a relative contraindication due to the cost and complexity of managing diabetes and pancreatic enzyme replacement therapies.	5	D
Guidance Statement 2.2 TPIAT should not be performed in patients with specific medical conditions, including: C-peptide negative diabetes, type 1 diabetes, portal vein thrombosis, portal hypertension, significant liver disease, high-risk cardiopulmonary disease, or known pancreatic cancer.	5	D
Guidance Statement 3 The severity, frequency, and duration of pain symptoms, narcotic requirements, disability/impaired quality of life, residual islet function, rate of disease progression, and age of the patient should be considered in timing of the procedure.	5	D

A = Strong positive, B = Weak positive, C = Uncertain or equivocal, D = Weak negative, E = strong negative.

Preoperative Testing and Assessment

Patients considered candidates for TPIAT should be evaluated by a comprehensive multidisciplinary team that will evaluate and counsel the patient preoperatively and continue to provide care for the patient after the surgery. Endocrinologists, gastroenterologists, pain management specialists, anesthesiologists, psychologists, social workers, and nutritionists are all essential to assess and inform the patient and the patient's family about the procedure, its potential risks, and chances of success. The list of specialties is usually adjusted and coordinated by the surgeon based on the patient's health status, his or her social needs and other factors.

Educating the patient and the patient's family and providing them with realistic expectations is as important as executing a technically sound operation. If anything, the patient usually has suffered for a long time from pain and a low quality of life and is eager to proceed with surgery as quickly as possible. It then behooves the surgeons and the entire team to temper the patient's zeal and methodically assess all facets of the patient's condition before surgery.

Continued collaboration of the multidisciplinary team members is also important after surgery: TPIAT success is defined as independence from pain medications, none or minimal requirement of insulin without any hypoglycemic complications and improved QOL enabling the patient to get reintegrated into the workforce. To achieve these goals, the patient needs to continue to work with the team members over months and sometimes years.

Routine blood tests including a hypercoagulable test panel are performed. CA 19-9 and carcinoembryonic antigen (CEA) levels are checked to rule out malignancy in the setting of CP. These patients often have undergone multiple CT and MRI studies in the past, but it is essential to rule out any bout of acute pancreatitis a week before surgery to avoid operating in the acute setting. Assessment of glycemic control, and thereby of islet cell function, is the key in the laboratory evaluation process. This is generally done by checking hemoglobin A1C as well as fasting and stimulated c-peptide levels, and performing glucose tolerance test and/or continuous glucose monitoring (based on the individual center's preference). In multivariate logistic regression modelling, metabolic measures correctly predicted insulin independence in about 70% of patients at 1, 3, and 5 years after TPIAT. Hence, metabolic testing measures before surgery are highly associated with diabetes outcomes after TPIAT at a population level and correctly predict outcomes in approximately two out of three patients [40].

TP results in surgically induced diabetes. Diabetes as the result of a TP or due to chronic pancreatitis, differs from type I DM in that this form of diabetes (Type 3c) is even more brittle due to the absence of insulin counter-regulatory hormones (glucagon, somatostatin). These patients are at high risk for developing hypoglycemic unawareness with an annual mortality rate of 2%–8%.25 However, one study found no mortality related to hypoglycemia in a series of 166 patients. Of note, two of these patients required a whole organ pancreas transplant to manage their brittle diabetes [41]. Without IAT, the mortality for TP has been reported to range from 0% to 8%, and its morbidity from 25% to 45% [42]. As part of the consent process it is important to make the patient aware of the magnitude of the procedure and its potential complications.

Operative Technique

Total Pancreatectomy – Principles: In patients undergoing TPIAT the whole pancreas should be removed en-bloc (i.e., without division at the neck as for other indications) [Fig. 2]. We previously described this technique in detail with preservation of blood flow to the pancreas via the gastroduodenal, splenic artery, and splenic vein until shortly before removal of the gland to avoid ischemic damage to the islets [Fig. 2]. A "sling" maneuver is used to facilitate the separation of the uncinate process from the portal and superior mesenteric (SMV) veins (Fig. 3 and 4). The spleen is preserved if possible ("Sutherland" technique). A duodenum-preserving pancreatectomy with standard gastrointestinal (GI)-reconstruction (duodenojejunostomy, hepaticojejunostomy, and if required jejunojejunostomy) is performed [43]. The islets are usually infused into the portal vein via the splenic vein or any other tributary stump of the portal vein [43].

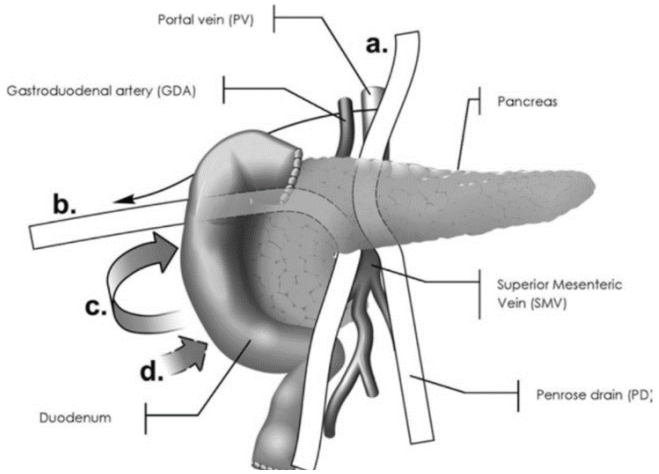


Figure 3: Schematic Drawing of the Principles of the Sling Maneuver.

Preoperative preparation

In preparation for surgery, patients usually undergo a full bowel prep the day before surgery and are kept nil per os (NPO) starting at midnight. The patients are usually admitted on the day of surgery and are reevaluated by the anesthesia and surgery teams.

In the operating suite, patients are placed in the supine position, with one arm (or both arms) tucked and the other at a 90-degree angle. Proper positioning allows the anesthesiologists' access to the patient, while not impeding surgeons' access to the frame of the operating room table, required to affix a self-retaining retractor. After administration of general anesthesia, central venous and arterial lines are placed. Preoperative doses of antibiotics (preferably meropenem, vancomycin, and fluconazole) are administered intravenously.

An assembly for delivery of the islets and portal vein measurements is prepared. Up to 6 three-way stopcocks are connected in series (see below). The outermost connection is reserved for connection to the prepared islets via a filterless IV line. The inner most (proximal towards the incision) is reserved for connection to the cannulation of the splenic vein stump. A standard IV extension set can be used. This is connected to a saline manometer for intermittent measurement of portal pressure and, and two 60 cc syringes to maintain pressure gradient and flush.

Operative Procedure

Access to the abdominal cavity is obtained by either a midline incision or a transverse incision in the upper and mid abdomen. The choice of incision is dependent on the patient's body habitus, as leaner patients may have narrow costal margins. Retraction can be achieved with either Thompson retractors (Thompson Surgical Instruments Inc.) or Omni-Tract retractors (Omni-Tract® Surgical).

After general evaluation of the abdominal cavity, a Kocher maneuver is performed with complete mobilization of the duodenum and pancreatic head to expose the left border of the retro-pancreatic inferior vena cava (IVC). The plane between the anterior surface of the duodenum and pancreas and the transverse mesocolon is entered to visualize the superior mesenteric vein (SMV). The anterior surface of the uncinate procedure is mobilized and carefully separated from the SMV. The gastrocolic ligament is then opened to enter the lesser sac. Care is taken to preserve the right gastroepiploic artery and short gastric veins in order to protect the accessory blood supply to the spleen after ligation of the distal splenic artery and vein. This is done in an effort to maintain vascular flow to and from the spleen and to avoid splenectomy if possible. Once the lesser sac is opened, the pancreas is assessed. Dissection is started at the lower border of the uncinate process of the pancreas and the anterior surface of the SMV is cleaned. Dissecting proximally, the pancreatic neck is separated from the SMV and elevated to view the tunnel beneath it. The tunnel is dissected as far cephalad as safely possible at this stage.

Dissection continues on the superior aspect of the duodenum and pancreatic head. The gastroduodenal artery (GDA) is identified. The right gastric artery may be ligated and divided. The GDA is looped. Preservation of pancreatic blood supply is key to minimize warm ischemia time, prevention of islet stress and preservation of islet viability and function [44].The common bile duct is identified posteriorly and laterally to the GDA. A loop is placed around the common bile duct.

The anterior portal vein above the pancreatic head is then dissected out. A tunnel posterior to the pancreatic neck is created on the anterior surfaces of the SMV at the level of the suprapancreatic portal vein and the uncinate process. The pancreatic neck is then looped with a penrose drain in preparation of the "sling maneuver" (Fig. 3 and 4). The head of the pancreas all the way to the neck is now completely freed from all fibrous attachments.

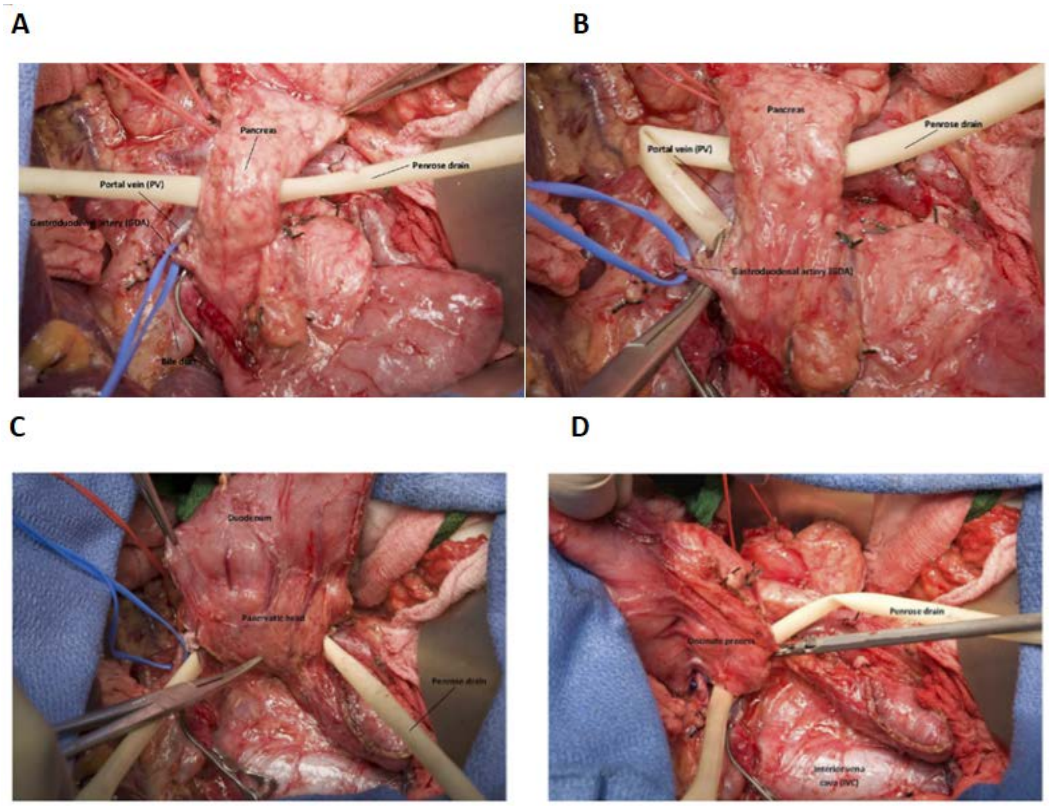
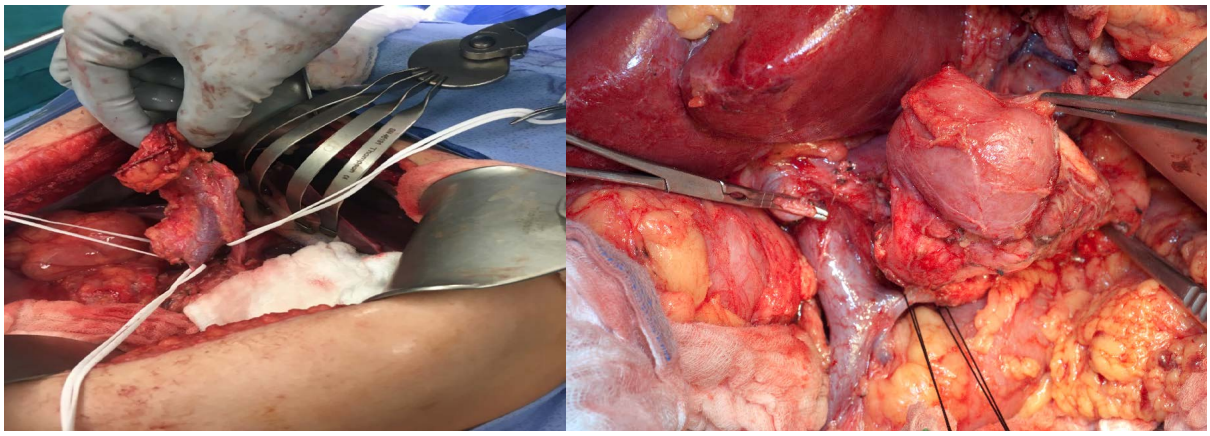


Figure 4: (A) Penrose Drain Below Pancreatic Neck, Anterior To Portal Vein; Loop Around The Gastroduodenal Artery (Gda); (B) Penrose Drain To Be Moved To Right Of The Gda; (C) Duodenum Rotated Medially; (D) Dissection Continues Over Penrose Drain.

Next, the dissection of body and tail of the pancreas along the inferior border of the pancreas lateral to the SMV is performed. The inferior mesenteric vein (IMV) is identified and ligated at its entrance into the splenic vein. If the IMV drains into the SMV, it can, but does not have to be ligated and divided. At the level of the middle of the body of the pancreas, the entire gland with the splenic vessels is circumferentially dissected free from the retroperitoneum and a vessel loop is passed around this tunnel for greater traction in an effort to widen the gap between the pancreatic tail and the spleen. Dissection is continued laterally and the splenic hilum is divided with an endovascular stapler if there is a large enough plane between the pancreatic tail and the splenic hilum. The tail of the pancreas is lifted up medially from its retroperitoneal attachments toward the confluence of the portal vein-SMV and the celiac artery.

At this stage, the splenic artery is traced to its takeoff from the celiac trunk and the splenic vein to its insertion into the SMV. Both vessels are looped (Fig. 5). Remaining tissues medial to the splenic artery at the superior border toward the portal vein are taken down using electrocautery. The entire body and tail (as the head before) are completely freed from all fibrous attachments.



(A) (B)

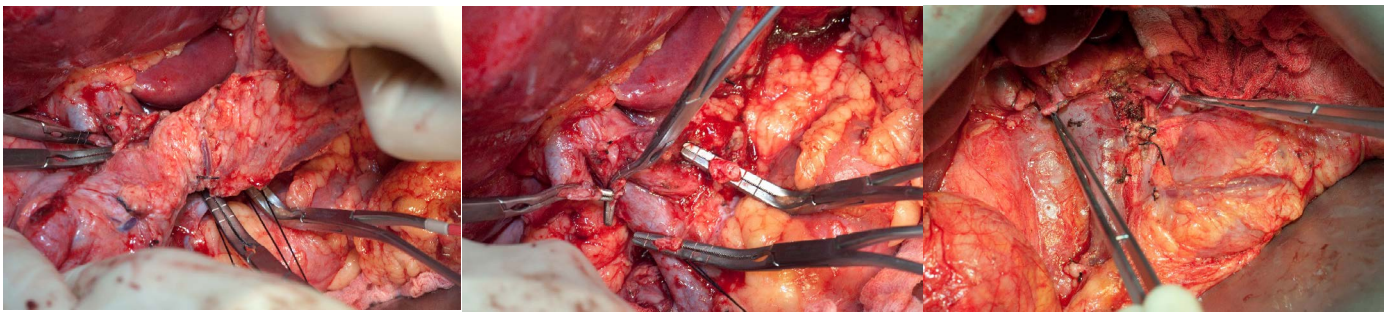
Figure 5: (A) Tail Of Pancreas: Splenic Artery And Splenic Vein Near Confluence With Portal Vein Are Encircled After Complete Medial Mobilization Of The Pancreatic Body And Tail Following Stapler-Transection Of Splenic Hilum; (B) Head Of Pancreas: Moved Medially Along With The Duodenum Exposing The Portal And Splenic Veins; The Bile Duct Is Already Transected And Clamped.

The pylorus is dissected and 2–5 cm of the first portion of the duodenum distal to the pylorus is preserved after division with a gastrointestinal anastomosis (GIA) stapler. The bile duct is then divided and proximally occluded with a soft bulldog clamp. The distal end is ligated or oversewn to prevent spillage of bile.

A GIA stapler is used to divide the jejunum about 20cm distal to the ligament of Treitz. The jejunal mesentery is mobilized and divided in such a way that adequate vascular supply is preserved to the distal jejunal end. The proximal end of the jejunum is brought to the right side from behind the main mesenteric vessels. This loop may be further shortened by GIA stapler at the level of second and third part of duodenum for the ease of uncinate dissection.

The previously placed penrose drain behind the pancreatic neck is brought behind the GDA and pulled laterally. The duodenum and the bottom end of the uncinate process are reflected medially (Fig. 3 & 4), exposing the penrose drain with the lateral wall of the portal vein and SMV [43]. The penrose drain basically functions as a sling (thus, 'sling maneuver'). This allows for easy separation of the uncinate process from the SMV (Fig. 3 & 4). It also protects the superior mesenteric artery (SMA) since no lymph node dissection is required as in a pancreatic cancer operation. Various energy devices as per surgeon's comfort can be used to dissect this area.

At this stage, the pancreas is only attached via the GDA, splenic artery, and vein (Fig. 5 & 6). The patient then receives 50 IU/kg of intravenous heparin. The GDA, splenic artery, and vein are individually clamped and divided. Their proximal stumps are carefully oversewn using 5-0 or 6-0 prolene sutures. Protamine is administered intravenously to neutralize the heparin effect.

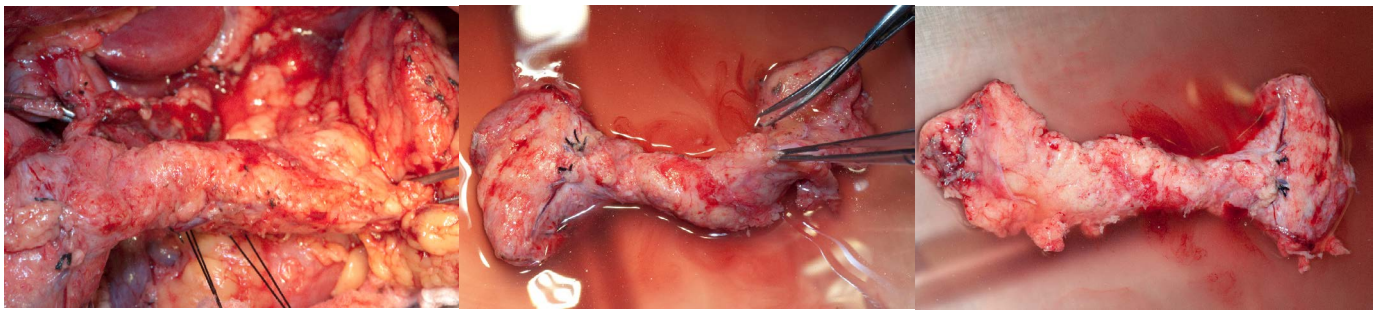


(A) (B) (C)

Figure 6: (A) Pancreas In-Situ After Clamping Of The Vessels And After Bile Duct Transection; (B) Pancreas Is Removed With Clamps On (From Right to Left) Common Bile Duct, Gastroduodenal Artery, Splenic Vein and Splenic Artery; (C) Pancreas and Clamps Removed.

The pancreas is removed and prepared on the back table [Fig. 7]. I usually flush the GDA, splenic artery, and the pancreatic duct with 20-50ml of University of Wisconsin (UW) cold storage solution at 4°C in similar fashion as a donor pancreas. The pancreas is then packaged and handed over to the isolation team. The isolation procedure as originally described by Ricordi remains the preferred method [7].

Gastro-intestinal continuity is re-established next. A Roux-en-Y duodeno-jejunostomy (or gastro-jejunostomy in case the pylorus in not preserved) is then performed in an end-to-side fashion with two layers, the inner layer with absorbable 4-0 PDS sutures and the outer layer with 4-0 silk or prolene sutures. A hepatico-jejunostomy or choledocho-jejunostomy is constructed in an end-to-side fashion using a single layer of interrupted 5-0 or 6-0 absorbable (PDS) sutures, about 40-60cm distal to the duodeno-jejunostomy. The jejunal Roux-en-Y loop is usually brought through an opening in the transverse mesocolon. This loop is secured with interrupted 4-0 silk sutures. If 2 Roux-en-Y loops are used (one for the anastomosis to the duodenum or stomach, the other to the bile duct), an additional jejuno-jejunostomy needs to be created [43].



(A) (B) (C)

Figure 7: (A) Pancreas Shortly Before Removal; (B) Front of Pancreas and Duodenum Immersed In UW Solution; (C) Back Of Pancreas with Stapled Tail (Left).

At the discretion of the surgeon or in the presence of anatomical variance(s) and/or intraoperative surgical complications it may not be feasible to remove the whole pancreas en-bloc. Transection of the pancreas may be required to facilitate removal and the two pieces (head/body with duodenum and tail) are sent separately for islet isolation. In this situation, the key to successful islet isolation remains preservation of the vascular supply until shortly before the pieces are removed.

In patients with previous pancreatic surgery, completion pancreatectomy can be quite challenging due to adhesions and scarring. If a Whipple procedure was performed in the past, the pancreatico-jejunostomy needs to be taken down and the jejunal stump closed. There is usually no need to revise the previous GI-reconstruction. If a distal pancreatectomy had been performed, a standard (completion) Whipple procedure is performed with standard GI-reconstruction as described above.

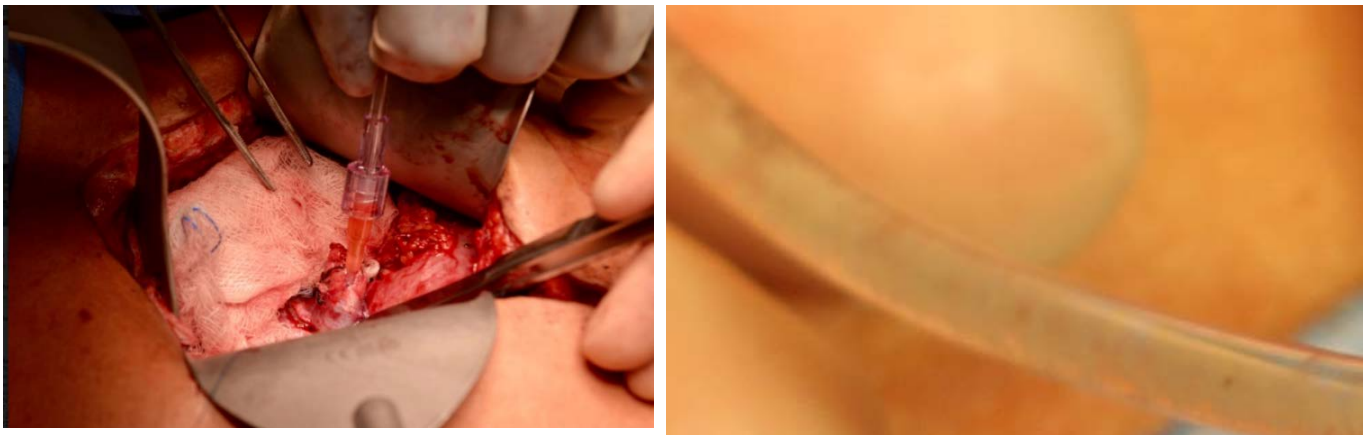
Intrahepatic Islet Infusion/Transplantation

If islet isolation is performed at the same facility, this procedure is started before or at the time of gastrointestinal reconstruction. If performed at an outside facility, as previously reported by our group, the pancreas is submerged in UW preservation solution and chilled at 4 degree C [45]. Any pre-existing ductal stents are removed and sent for culture. The pancreas is then packaged per UNOS guidelines in 3 bags. The patient's abdomen is closed and the patient is extubated. The patient will return to the operating room after arrival of the islet isolation product. Alternatively, the infusion may be performed by interventional radiology.

Prior to islet infusion, Etanercept 50 mg IV, and Anakinra 100 mg subcutaneously, and a heparin bolus of 35 units/kg (islet drip also contains 35 units/kg heparin) are administered [4]. Etanercept, a tumor necrosis factor (TNF) inhibitor and Anakinra, an interleukin (IL)-1 antagonist serve as anti-inflammatory agents to improve islet grafting and are of-

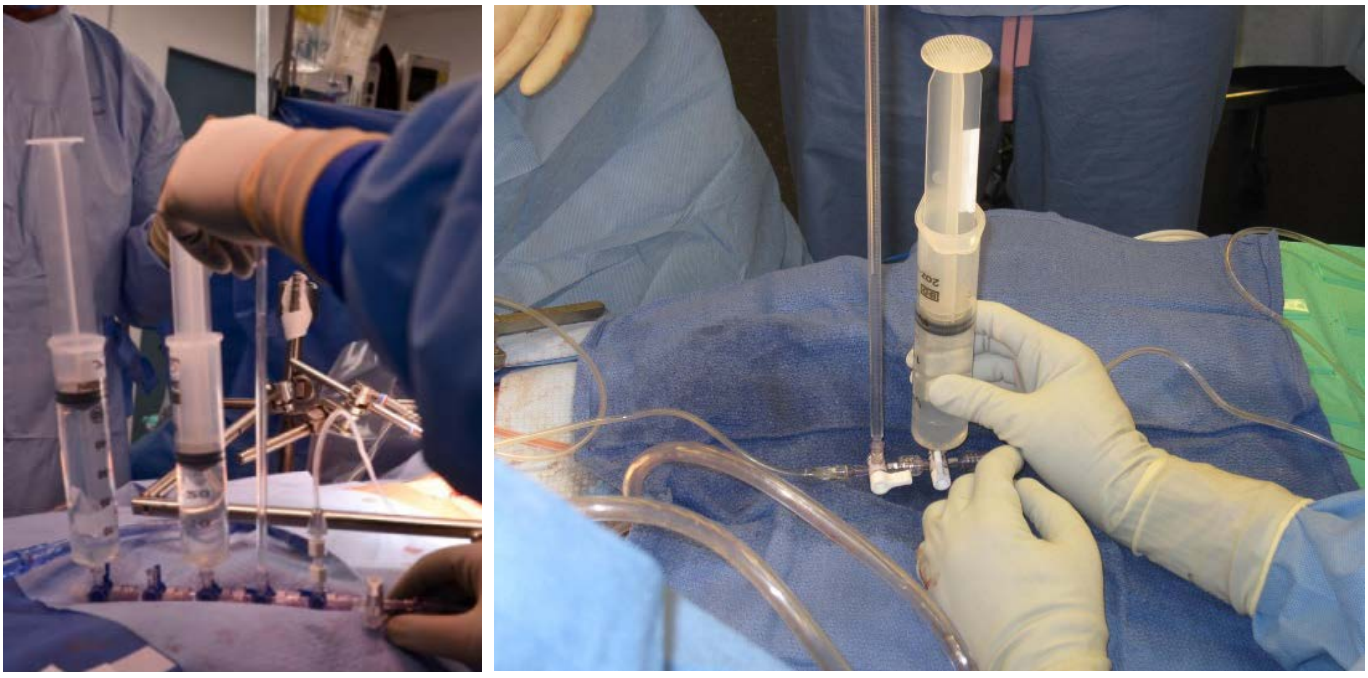
ten used in islet allotransplantation. There is some evidence that these drugs have similar effects in autotransplantation [46, 47]. The use of Anakinra potentiates the effect of Etanercept, leading to improved insulin content and reduction in apoptosis as shown in animal studies [48]. Heparin is added to prevent thrombosis of the portal vein and its branches as well as clumping of islet cells.

After the process of islet isolation is completed, the islets are infused in the operating room. The liver via portal vein infusion serves as the engraftment site. In preparation, a stay suture using 6-0 polypropylene is placed on the splenic vein stump (or any other portal vein tributary such as the IMV). A 14F angiocath is then introduced and can be secured with the stay suture or held in place (Fig. 8). Using the previously described assembly (Fig. 9) the islets are infused and the portal pressure is measured. The portal vein pressure should be measured at baseline and then intermittently assessed before infusion and about every 10-15 min during infusion. If the portal vein pressure is greater than 25–30 mmHg, islet infusion should be halted for a while until the portal vein pressure drops. If it does not drop, the duodenal wall, the omentum, and the cul-de-sac have been used as additional engraftment sites [4].



(A) (B)

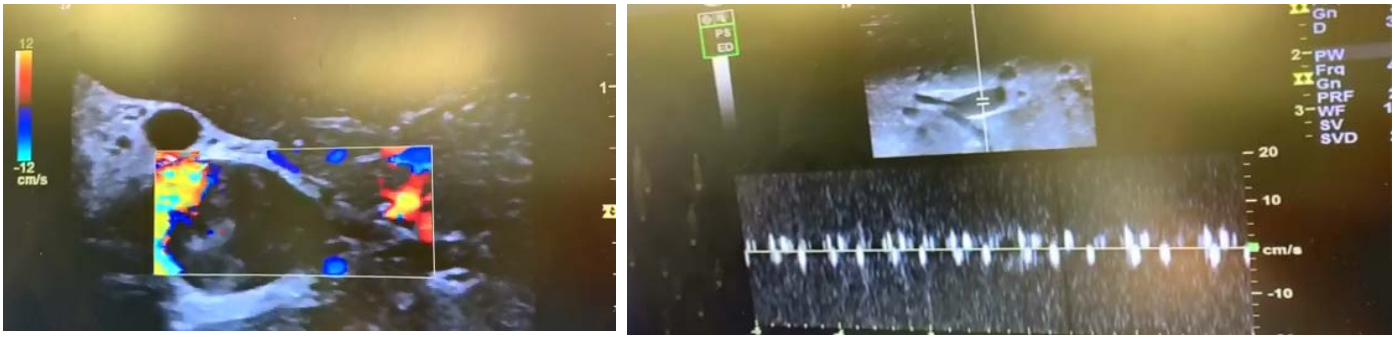
Figure 8: (A) 14-Gage Angiocatheter in the Splenic Vein Stump; (B) Visible Islet Cell Clumps.



(A) (B)

Figure 9: Assembly For Transfusion Of Islet Cells And Portal Vein Measurement With 6 (A) Or 3 (B) Three-Way Stopcocks Connected In Series.

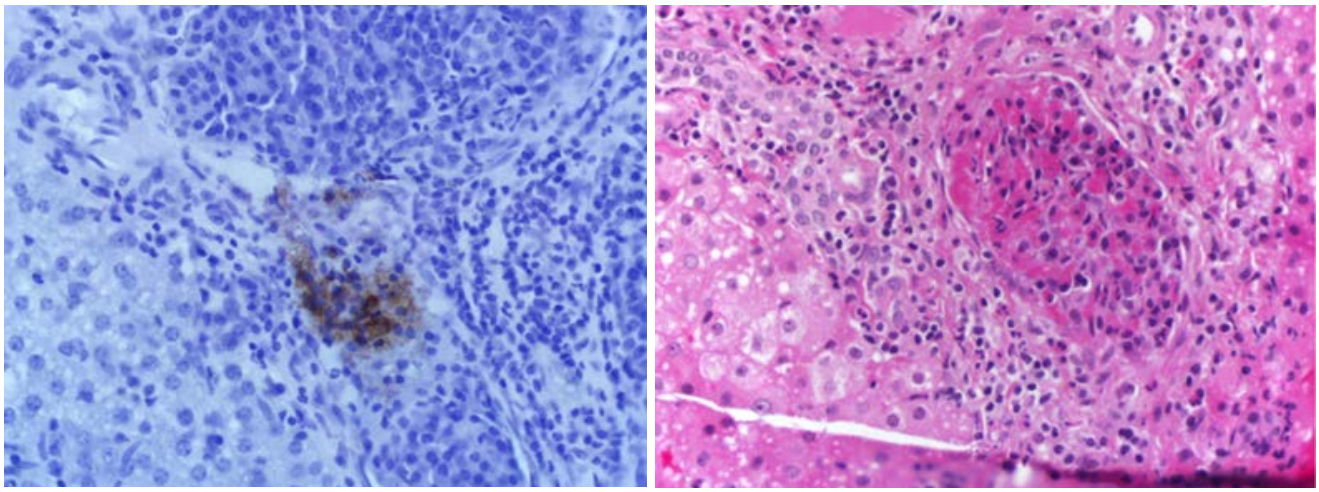
We have described an alternative to portal vein pressure monitoring: real-time, intraoperative Doppler/ultrasound monitoring of the islet infusion into the liver via the portal vein [49]. We have used continuous real-time Doppler ultrasonography during the islet infusion to study portal vein and intrahepatic flow patterns, as well as changes in Doppler signals (Fig. 10). Flow and signal changes may allow for timely adjustment of the infusion rate, before a marked increase in portal vein pressure is noted and decrease the risk of portal vein thrombosis [49].



(A) (B)

Figure 10: Real-time, intraoperative Doppler/ultrasound monitoring of the islet infusion into the liver via the portal vein. (A) Infused islets are seen on the right in the portal vein. (B) Real-time intraoperative Doppler study of the portal vein. Flow and signal changes allow for timely adjustment of the infusion rate, before a marked increase in portal vein pressure is noted.

At the end of the infusion, the cannula is pulled out, the prolene stay suture is tied and hemostasis confirmed. Core liver biopsies of the right and left lobes of the liver are obtained before and after infusion of the islets. They provide a baseline assessment about the histopathology of the liver specifically if an unusual elevation of liver enzymes is noted postoperatively. These biopsies frequently demonstrate engraftment of the islets within the portal venous system [Fig. 11].



(A) (B)

Figure 11: (A) H&E stained auto-islet in native liver after transplantation via splenic vein. (B) IHC stain for insulin on auto-islet transplantation.

After islet infusion, a gastric or jejunal feeding tube may be placed, especially in patients with a poor nutritional status. Before the abdomen is closed in standard fashion, the viability of the spleen is reassessed. If tears, bleeding or swelling of the spleen are noted then a splenectomy should be performed. Prophylactic vaccinations include polyvalent pneumococcal vaccine (Pneumovax 23), Haemophilus influenzae b vaccine (HibTITER), and meningococcal polysaccharide vaccine prior to discharge when medically stable [49].

Drains are usually placed as per the surgeon's discretion, but it is not uncommon to place 2 Jackson-Pratt (JP)-drains, one in the pancreatic bed toward the spleen and another in Morrison's pouch behind the hepaticojejunostomy. Some centers in Europe have been reported successful islet autotransplantation into straited muscle, i.e. intramuscular autologous transplants [50-53]. However, this technique is not widely practiced.

When technical limitations prevent complete intraportal/intrahepatic transplantation, an omental pouch can be created to contain the remaining islet mass. The omentum has potentially desirable qualities such as accessibility, capacity, and systemic/portal vascularity comparable to the native pancreas. At 3 months follow-up there were no significant differences in glycemic control or graft function for the com-

bined site recipients compared with their matched controls who only received an intraportal islet infusion [54].

Percutaneous Islet Infusion/Transplantation

Interventional radiology can also assist with infusion of islets. This method is useful in patients undergoing delayed infusion of islets, for example, in facilities without on-site isolation capabilities. Percutaneous islet infusion was first performed in 1999 by Weimar et al. who utilized computed tomography and fluoroscopic techniques to cannulate the portal vein [55]. Since then sonographic techniques have also been described, demonstrating low complication rates and adequate long-term results [56].

Difficulties and complications associated with percutaneous islet infusion include repeated attempts at cannulation, bleeding, hemoperitoneum, hemothorax, and portal vein thrombosis. The major advantage for patients undergoing percutaneous infusion is that they do not require general anesthesia. Sedation with versed and fentanyl usually suffices. Using fluoroscopy or ultrasound guidance, an appropriate puncture site is identified, and local anesthesia is administered. A branch of the right portal vein is identified and accessed with a 22-g Chiba needle as described by Owen et al [57]. An 18g guidewire is introduced and advanced to the portal vein. A sheath is then advanced over the wire to the portal confluence. Under fluoroscopy, a venogram is performed to confirm correct placement. Islet infusion is conducted as previously described with frequent assessment of portal venous pressure measurements. Embolization of the tract with a gelatin sponge has been described, however, with smaller catheters has been performed less often. Postoperative care consists of bed rest with follow-up ultrasound of the portal vein [57]. Percutaneous islet infusion is not a common procedure. Due to its additional technical requirements and increased resource utilization, most surgeons prefer intra-operative infusion under direct vision.

Minimally Invasive Surgery

TPIAT using minimally invasive techniques has also been described. Giulianotti et al. described the first robotic distal pancreatectomy with IAT in 2009, in a patient with CP. The islets were transfused via a mesenteric vein; the robot was not used for the infusion the first robotic TP for a patient with CP was described in 2010 by Marquez et al [58]. The islets were obtained from the distal pancreas specimen and transfused through a Pfannenstiel incision via a mesenteric vein of a small bowel loop [59].

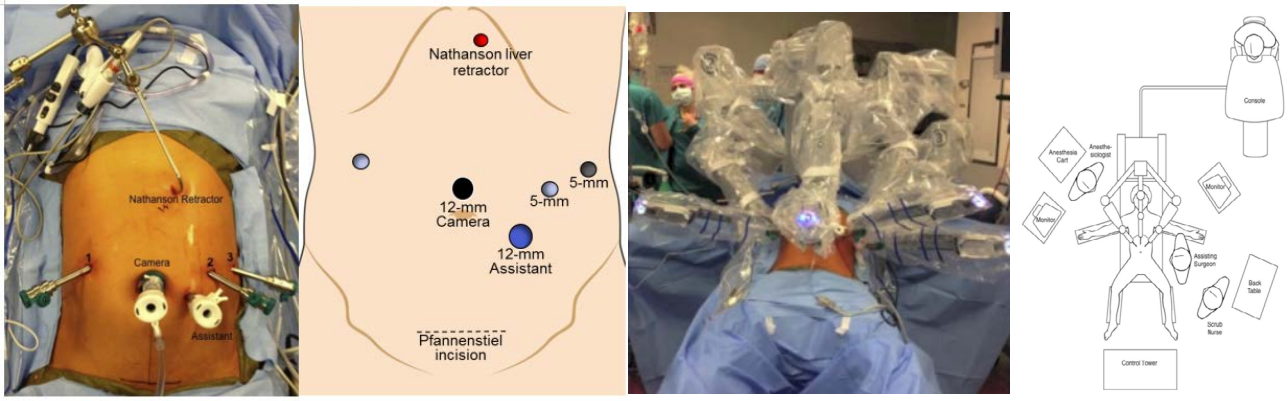
The first fully robotic TPIAT, using the Da Vinci system for both pancreatic resection and islet infusion, was performed by Galvani et al. at the University of Arizona in 2013 [60]. The first series of robotic TPIAT using the whole pancreas was also first reported by Galvani et al. in 2014 [61].

Laparoscopic TP was described later, with the first two fully laparoscopic pylorus and spleen preserving total pancreatectomies reported in 2013 by Dallemagne et al. for IPMN and neuroendocrine lesions [62]. Fan et al. described the first series of laparoscopic TPIAT in 2017. Their technique involves resection of the pancreatic head and duodenum followed by a distal pancreatectomy. Conversion to open was required in two out of their 20 patients due to difficult anatomy and prior surgery [63]. The islets were transfused via a 14–18 g laparoscopic needle using a 12-mm trocar into the splenic vein stump.

A case-matched study of 42 pediatric patients with laparoscopic-assisted versus open TPIAT showed comparable outcomes and similar surgical complications in both groups. The authors concluded that in children, a minimally-invasive approach does not compromise safety, effectiveness, or operative efficiency [64].

Robotic Tp and Islet Autotransplant

Except for minor changes, the principles for robotic TPIAT are the same as for open TPIAT [60, 61, 65]. The patient is placed in the supine position with both arms tucked. After induction of general anesthesia, arterial and central vein lines are placed. The operating table is rotated in such a way that it allows for docking of the robot from the patient's head. Ports are placed as depicted in (Fig. 12). Prior to docking of the robot, the gastrocolic ligament is taken down laparoscopically.



(A) (B) (C) (D)

Figure 12: (A And B) Port Placement For Robotic Tpiat; (C And D) Docking Of Davinci Si And Positioning Of Intraoperative Personnel.

A Nathanson retractor is placed to retract the stomach anteriorly. Next, the robot is docked from the head of the patient.

In the robotic procedure, the tail of the pancreas is mobilized first, along with dissection of the splenic artery and vein [4, 60]. The space between pancreatic tail and spleen is divided using an endovascular stapler. The blood supply to the tail of the pancreas via the splenic vessels is preserved until final en-bloc removal of the pancreas in order to minimize warm ischemia of the islets. All retroperitoneal attachments of the distal pancreas are taken down. The splenic artery is dissected at its take-off from the celiac trunk and the splenic vein at the confluence with the SMV.

The right colon and duodenum are mobilized. An extended Kocher maneuver is performed providing exposure to the SMV. The uncinate process is separated from the superior mesenteric vessels by dividing all venous tributaries with the harmonic scalpel or by suture ligation. The first portion of the duodenum is divided proximally with a linear cutting stapler roughly 3–5 cm distal to the pylorus, followed by division of the common bile duct. The pancreas is then completely mobilized, attached only by its vascular pedicle.

After administration of intravenous heparin (50–70 IU/kg), the splenic artery, GDA, and splenic vein are divided using an endovascular stapler. The splenic vein is divided approximately 3 cm proximal to the confluence to leave a relatively long stump for the islet infusion. Protamine is administered intravenously to neutralize the heparin effect. The pancreas is then removed via a 6–7 cm Pfannenstiel incision. As in open surgery, the spleen is only removed if does not appear viable, as the right gastroepiploic and short gastric vessels usually remain intact. While the gastrointestinal reconstruction takes place, the islets are isolated in the laboratory.

A hepaticojejunostomy using running 4-0 polydiaxanone sutures is performed. The duodenojejunostomy is performed with 3-0 V-Loc sutures in two layers, 50 cm from the hepaticojejunostomy. A modified jejunojejunostomy Braun anastomosis (to reduce bile reflux gastritis) can also be performed using a GIA stapler. The mesenteric defects are closed with 3-0 V-Loc sutures [4, 60, 61].

Laparoscopic Tp and Islet Autotransplant

A 12-mm port is placed in the umbilicus [63]. An additional 12-mm port is placed on the right and a 5-mm port on the left side of the abdomen. The gastrocolic ligament is divided. The GDA is identified, ligated, and divided. A tunnel is created posterior to the neck of the pancreas, with dissection of the portal and SMVs. The first portion of the duodenum 3–5 cm distal to the pylorus or a distal gastrectomy is performed using an EndoGIA stapler. A cholecystectomy is performed. The neck of the pancreas is divided, followed by a pancreaticoduodenectomy.

As described by Fan et al., the head of the pancreas is then given to the extraction team and processed. Thus, the pancreas is not removed en-bloc. The distal pancreas is removed separately, after division of the splenic artery followed by the splenic vein. The specimen is also sent for islet isolation processing. A hepaticojejunostomy is performed using 4-0 barbed sutures and suture clips. A standard jejunojejunostomy is performed. The islets are infused via the portal vein using a 16 g needle via a 12-mm port site [63].

Robotic and Laparoscopic Tp Outcomes

Outcomes in minimally invasive TP with or without IAT are limited to small volume (n < 20) case series. While outcomes in minimally invasive procedures are comparable to the open technique in terms of complications, it was noted in one study that the mean islet count per kilogram was reduced (1325 IE/kg in the laparoscopic series, 2592 IE/kg in the robotic series compared to > 3000 IE/kg in open series) [64]. This may be very well related to prolonged warm ischemic effect on islets due to early ligation of vessels as well as the inflammation induced by dividing the pancreas during removal [44]. Robotic-assisted procedures although noted to have increased operative times (600 vs 469 min, P = .014), had less blood loss (220 vs 705 cc, P = .004) [63, 65, 66]. In a direct comparison of robot-assisted TPIAT compared to open, there were no significant differences in outcomes [65]. Further long-term and greater power studies are needed to further characterize the role of robotic TP.

Postoperative Care

Postoperatively, patients are admitted to the intensive care unit. The nasogastric tube is left in place. Patients are maintained on an intravenous insulin drip postoperatively "to rest the islets", with a goal of titrating blood sugar levels between 80 and 120 mg/dL. Pain control can be achieved via narcotics, parenteral acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), lidocaine infusion, and/or fentanyl patch. Consultation from the pain management and anesthesia teams is crucial since many CP are dependent on opioid drugs. Thus, the pain management team needs to follow the patient closely throughout the hospitalization. If gastrostomy and jejunostomy tubes are present, they are placed to gravity. Antimicrobial prophylaxis with meropenem, vancomycin, and fluconazole is administered for 7-10 days and discontinued if cultures are negative.

Anticoagulation is very important in the immediate post-operative period to mitigate the phenomenon of Instant Blood-Mediated Inflammatory Reaction (IBMIR), a process marked by platelet adherence and leukocyte infiltration to the islets [67]. It also prevents the dreaded complication of thrombosis in the portal venous system. Heparin is the most common agent used intravenously, followed by conversion to low molecular weight heparin. When unfractionated heparin (UFH) versus enoxaparin were compared for prevention of postoperative portal vein thrombosis, no difference was observed, but enoxaparin was associated with an overall higher incidence of other thrombotic complications of note, a study in children who underwent TPIAT showed that islet graft failure was less likely at 1 and 2 years when low-molecular-weight dextran was infused postoperatively [68]. Dextran use was overall safe, although it did lead to a higher incidence of postoperative bleeding requiring blood transfusions [69]. Despite the use of aggressive anticoagula-

tion protocols in the immediate postoperative period, serial vascular ultrasound studies of the abdomen are obtained to assess portal vein patency.

Postoperatively, the patient receives Anakinra 100 mg SC on postoperative days 1–7. Etanercept is given on postoperative days 3, 7, and 10 (if still in hospital). As previously noted, Anakinra and Etanercept work in concert to reduce inflammation and improve islet graft survival and function [46-48].

The patient can be started on total parenteral nutrition (TPN) postoperatively per institutional guidelines if the patient was nutritionally very weak to go into surgery. With guidance from endocrinology, patients are started on long acting and pre-meal doses of insulin, a regimen that is continued for several weeks, in order to rest the implanted islets. Close outpatient follow-up by the endocrinologists is essential for titration of the insulin regimen. Nasogastric tube and enteral nutrition can be gradually started. For patients who become independent from insulin, C-peptide levels are obtained monthly during postoperative follow-up to assess function of the transplanted islets.

Pancrelipase (Creon, Pancreaze, Pertzye, Ultresa, and Zenpep) is also used liberally after TPIAT. One of the manufacturer's recommendation (Creon ®) post-pancreatectomy per meal dose is 72,000 units, however, we titrate the dosage based on the improvement in patient steatorrhea.

Complications

The rate of postoperative complications after TPIAT ranges widely in the literature. Though previously reported as high as 30%–40%; the rate has significantly decreased with increasing experience and volume [70, 71]. Complications of TPIAT include, but are not limited to, portal vein thrombosis, delayed gastric emptying, intra-abdominal abscess, intra-abdominal hemorrhage, GI bleeding, sepsis, hypoglycemia, wound complications, vitamin/ bone density changes, and islet contamination. Of note, postoperative complications after TPIAT were in one study associated with longer hospital and intensive care unit stays and with a higher readmission rate; however, the surgical complications did not affect islet graft function. [72].

Portal Vein Thrombosis

High portal pressures after completed infusion is risk factor for portal vein thrombosis. Large tissue volume (TV) is also a risk factor in the development of portal vein thrombosis. Purification of islets is dependent on a series of gradients; therefore, the yield and purity of islets can be variable. Wilhelm et al. recommended that a TV < 0.25 cc/kg is recommended during islet manufacturing [73].

A large study involving 409 TPIAT patients suggested that portal vein thrombosis may be more strongly associated with islet infusion than extreme thrombocytosis after TPIAT. Thromboembolic events occurred in 12.2% of patients, with portal vein thromboses occurring significantly earlier than peripheral thromboses. Perioperative heparin was given to all patients. Interestingly, 67% of TPIAT patients developed extreme thrombocytosis (platelets ≥1000 × 109/L), peaking around postoperative day 16, and extreme thrombocytosis was significantly associated with infused islet volumes. Most thromboembolic events (82.7%) occurred before the postoperative day of maximum platelet count. Portal vein thromboses were associated with infused islet volumes and portal pressures but not platelet counts or other measures [74].

Postoperative treatment of reactive thrombocytosis using aspirin in adults and hydroxyurea in children was not associated with significantly decreased thromboembolic risk [74]. Real-time, intraoperative Doppler/ultrasound monitoring of the islet infusion into the liver via the portal vein is a new tool that may help to decrease the risk of portal vein thrombosis [49]. It allows to study portal vein and intrahepatic flow patterns directly during the infusion and may allow for timely adjustment of the infusion rate, before a marked increase in portal vein pressure is noted with the risk of portal vein thrombosis [49].

Although portal vein thrombosis is one of the most serious complications after TPIAT, its overall incidence is probably low (<5%) as more recent studies have shown [75]. Some investigators have even suggested that portal vein thrombosis, in the setting of routine screening and anticoagulation therapy, is a self-limited process [68].

If portal vein thrombosis occurs intra-operatively, during the infusion, or within the first couple of days post-operatively resulting in surgical re-exploration, intra-portal administration of tissue plasminogen activator (TPA) or urokinase may be indicated along with thrombectomy.

If partial portal vein thrombosis occurs postoperatively and does not require surgical re-exploration, treatment still consists of aggressive anticoagulation. The creation of a mesocaval shunt is extremely rarely indicated if the diagnosis is timely and the therapy is quickly initiated. In most cases portal vein thrombosis resolves within 6 months after TPIAT [68].

Delayed Gastric Emptying

While the exact mechanism of dysmotility after TP is unclear, suggested factors include resection of the pancreatic head, duodenectomy, disruption of hormonal influences, and vagal nerve injury. Nonetheless, delayed gastric emptying can be found in up to 45% of patients postoperatively and has been shown to have a negative impact on QOL after TP, often causing prolonged length of stay and higher readmission rates [76]. Treatment includes use of prokinetics, avoidance of opioids, treatment of electrolyte abnormalities, and early ambulation [77, 78].

Biliary Anastomotic Leak

TPIAT involves creation of a hepaticojejunostomy which is at risk for leak. Management involves percutaneous transhepatic cholangiography (PTC) drainage, and possibly reoperation.

Other complications

A variety of other surgical and medical complications have been described after TPIAT. Gastrointestinal bleeding was noted in 12.4% of patients after TPIAT, most commonly anastomotic ulcer bleeds (35%); about one third of patients had an undefined etiology despite endoscopy. The need for intervention was high (30%) and included relaparotomy (10%), endoscopic treatments (19%) and open embolization (1%) [79].

Disseminated intravascular coagulation (DIC) is a rare complication reported in islet transplantation patients in the 1980s. Theories include the presence of tissue thromboplastin in the cell preparation as a precipitating factor [80, 81]. Although also rare, pancreatic tissue can embolize to the pulmonary system, and can also lead to DIC. Froberg et al., at the University of Minnesota, reported a case of a patient that went into DIC and expired [82]. Pathology showed pancreatic exocrine emboli in the pulmonary vasculature. The mechanism for this development is unclear, however, hypotheses suggest exposure of pulmonary vessels to exocrine enzymes in transfused pancreatic preparation contribute to the thrombogenic conditions leading to DIC.

Although rare, metastatic pancreatic adenocarcinoma after TPIAT has been reported. Patients with CP are at risk for pancreatic adenocarcinoma, which can be undetectable at the time of surgery. Muratore et al. reported a case of pancreatic adenocarcinoma arising in the native liver following TPIAT. The patient had normal CA 19-9 and carcinoembryonic antigen (CEA) levels prior to the operation. However, the patient had elevated levels of select microRNAs which can potentially be a modality to screen patients [83].

A variety of medical complications have also been described after TPIAT. Atypical steatosis patterns frequently develop after TPIAT, implying that the procedure itself is the causal factor. However, there appears to be no correlation between islet graft function and the presence or pattern of steatosis. Hence, an atypical pattern of hepatic steatosis can therefore be considered an incidental finding after TPIAT and does not require additional workup or treatment [37].

Fat-soluble vitamin deficiencies (vitamins A, E, D) are common among children undergoing TPIAT and are even more prevalent after TPIAT. Children should be monitored for FSV deficiency after TPIAT [84].

TPIAT is also associated with decreases in bone mineral density in the body, lumbar, and hip regions in the first year after TPIAT but these appear to stabilize between 12 and 18 months after TPIAT [85].

Islet Contamination

Microbial contamination of the islets is not uncommon given the continuity of the specimen with the duodenum and gastrointestinal tract. Factors contributing to contamination include long warm and cold ischemia times. It has been reported that over 30% of surveillance cultures during pancreas processing grew bacterial strains with predominantly polymicrobial contaminations (in 60%). In that study at least one positive culture was identified in almost half of the patients (46%) undergoing TPIAT and a third had both surveillance cultures positive. However, while infectious complications were common among TPIAT patients, no concordance between pathogens isolated from the pancreas and those identified during infection was found [86].

Despite contamination, graft function is usually not affected [87]. In a series of 251 patients from multiple centers that underwent sterility culture testing, 161 (61%) had positive cultures, of which only 7 (4.7%) went on to have infectious complications with the same organism isolated [88]. Treatment is according to the results of antibiotic sensitivity. Peri-operative antibiotics are continued for at least 7 days until preliminary cultures results are available.

Salvage or Completion Pancreatectomy

Given the concerns that TP causes surgical-induced brittle surgical diabetes, patients are initially often subject to partial pancreatic resections in an attempt to manage their pain and avoid a TP. One study reported that 29% of their patients had previous pancreatic surgeries [89].

Completion pancreatectomy and IAT remains an option for patients that have undergone previous pancreatic surgeries and continue to have pain. The patients' ongoing pain originates from remnant pancreatic tissue. Wilson et al. reported in their series of completion pancreatectomy with islet autotransplant that all patients had a reduction in their narcotic requirements, with 44% achieving narcotic independence, and that islet isolation was possible in all patients with an average yield well above 300,000 units per kg [42].

Pediatric Population

Children with CP are also candidates for TPIAT, with patients as young as 5 years old. Pediatric patients undergoing TPIAT usually suffer from acute recurrent pancreatitis (ARP) or CP, commonly associated with an underlying genetic mutation such as cationic trypsinogen (PRSS1), cystic fibrosis transmembrane conductance regular (CFTR,) and serine protease inhibitor Kazal type 1 (SPINK1). Opioid use is not uncommon in this population, as is depression [90]. In pediatric patients, younger age, no prior Puestow procedure, and higher islet yield were all associated with higher rates of insulin independence [91].

Early identification of these patients and avoiding delays into early adulthood can prevent psychosocial and learning issues that result from coping with the burden of this illness [90-92]. According to a report from the Prospective Observational Study of TPIAT, pancreatectomy techniques differ between children and adults. Children (vs. adults) significantly more commonly undergo splenectomy (100% versus 91%), pylorus preservation (93% versus 67%), Roux-en-Y duodenojejunostomy reconstruction (92% versus 35%), and enteral feeding tube placement (93% versus 63%). The median islet equivalents/kg transplanted is higher in children (4577; IQR 2816-6517) than adults (2909; IQR 1555-4479; $p < 0.0001$), with COBE purification less common in children

(4% versus 15%). Further, the rates of portal vein thrombosis and early readmission are lower in children [93].

The patients are followed in the pediatric ICU until weaned from the insulin drip. Outcomes in a recent series of 17 pediatric patients show up to 82% insulin independence, and 100% pain relief early studies suggest that islet yield can be predicted by fasting glucose and body weight which may be a factor in pediatric patients considering islet autotransplant. Bellin et al. suggest the following formula: Predicted total IE = 429,853 + 4563*(body weight, kg) – 6091 * (fasting plasma glucose, mg/dL) [92, 94]. Over the past few years, there has been mounting evidence that opioid, parenteral nutrition, and exogenous insulin use can successfully be weaned within 90 days after TPIAT in children, with gains in health-related quality of life [95].

Remote Processing

Off-site islet transplantation laboratories provide an opportunity for institutions without in-house islet isolation to offer TPIAT. The pancreas and islets can be transported even over long distances via charter jets. Centers using off-site laboratories report similar outcomes with regards to insulin independence and yield. Time from pancreatectomy to infusion has been described up to 11 h. Increased cold ischemia time as a result of remote processing may not influence islet yield [45, 96-98]. Protocols on shipping are center dependent.

Quality Of Life and Outcomes after Tpiat

All of our TPIAT had very poor quality of life preoperatively due to unbearable and chronic pain, frequent hospitalizations and nutritional deficiencies [17, 18, 65, 99]. In patients with CP, 74% report their work lives to be negatively affected by their underlying disease, thus limiting their ability to work which in turn results in frequent absences and eventually in loss of their jobs. CP also had an effect on social lives in 60% and impacted relationships with significant others in 46%. On visits to the ED, patients were often perceived as alcoholics or drug seekers [100].

In our experience, the vast majority of our patients also have significant improvements in quality of life. Studies investigating the quality of life use the short form questionnaires validated and developed by the RAND Corporation. In one of our studies using the SF-12 and SF-36 surveys and examining the quality of life in patients up to 12 months after TPIAT, overall results consistently demonstrate improvements in quality of life [99]. This and other studies have demonstrated improvements in mental health, including subscales that focused on social functioning and role-emotional. In addition to improvements in mental health, the physical component scores also were significantly improved, with patients reporting increased energy. Similarly, bodily pain scores significantly decreased. In alignment with the results of the surveys, we reported a decrease in visual analog pain scores (VAS) [85]. Morgan et al. and Solomina et al. showed a significant decrease in narcotic use in their respective patient cohorts [99, 101, 102]. Together with the clinical outcomes in TPIAT, these quality-of-life studies show the benefit of performing TPIAT. Most important are, however, actual patient testimonials. They show the true transition of a crippling to a fulfilling lifestyle [103].

Future

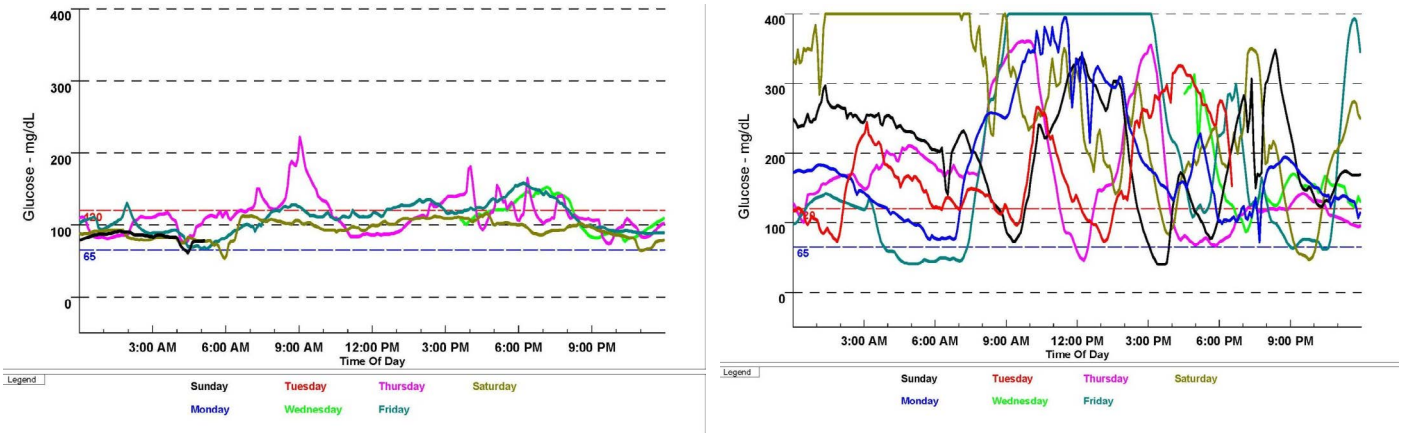
Like so many TPIAT patients have seen a very positive and lasting transformation of their lives, so has the field itself. TPIAT is now offered at an ever increasing number of centers in the Western world. Many insurance companies in the United States provide coverage for the procedure. The days when Dr. David Sutherland - who created the procedure – had to justify a “controversial” therapy or was even ridiculed at professional meetings about the validity of the procedure are long gone. Standard textbooks of surgery who did not even mention the procedure until late into the 1990s have added chapters to educate the next generation of surgeons on this topic. A plethora of peer-reviewed articles on TPIAT has been added to the literature over the past 5 years.

Future strategies in the field of islet auto transplantation will focus on advances of islet engraftment, alternative sites, increase in islet yield, and development of tissue-engineered islets. There appears to be exciting progress on the horizon specifically in the field of islet bioengineering and regeneration [104].

With regard to surgical techniques, it appears reasonable to predict that robotic and laparoscopic techniques will become more prevalent in the future and that open procedures will be performed primarily in patients with previous pancreatic surgeries or complex anatomy. Although data available today has not shown it yet, it is probably fair to predict that the duration of surgery and time of hospitalization will further decline with an increase in the number of minimally invasive procedures once surgeons rise above the relatively steep learning curve.

As to the disease itself, TPIAT will likely play an even more important role in the future for patients with disabling CP and eventually replace most of the partial resections and drainage procedures which leave diseased and pain-causing pancreatic tissue behind. Neither partial resections nor drainage procedures eradicate or cure this disease. The reported improvements in QOL after TPIAT are undeniable. Patients with chronic pain syndrome and preserved endocrine pancreatic function should only undergo surgery for CP at a center that also offers the islet autotransplant component. A TP alone, without the IAT component, in patients with normal (or near-normal) endocrine function can basically no longer be justified for scientific and ethical reasons.

Key to successful TPIAT outcome is early referral of the CP patient, i.e. once the disease has been diagnosed (Fig. 13). We continue to see patients who underwent innumerous ERCPs to no avail, previous surgeries to no avail and eventually present in a diabetic state when TPIAT is no longer an option. However, even for patients with very advanced CP, chronic pain syndrome and dependence on insulin there is another treatment option: TP with a subsequent pancreas transplant to resolve both exocrine and endocrine insufficiency [105].



(A) (B)

Figure 13: (A) Continuous Glucose Monitoring in a Patient after Total Pancreatectomy with Successful IAT; (B) Continuous Glucose Monitoring in a Patient after Total Pancreatectomy without IAT. (Courtesy Dr. Horatio Rilo)

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