A Technique for Total Pancreatectomy that Minimizes Warm Ischemia Time while Allowing Processing of the Whole Organ for Autologous Islet Transplantation

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Background	Total pancreatectomy combined with autologous islet transplantation (AIT) for chronic pancreatitis (CP) has been associated with the best outcomes in terms of pain relief and prevention of diabetes.
Summary	A safe technique to minimize warm ischemia time during pancreatectomy for CP was developed at our institution and is herein being presented. The pancreas was exposed to less than 1 minute of warm ischemia time. The islet isolation procedure resulted in 40ml of unpurified tissue containing 250,000 Islet Equivalents (IE). Long-term morphine medication and insulin treatment were withdrawn before discharge. At 1-year follow up the patient was insulin-independent wit normal Hemoglobin A1C (HbA1c) and pain medication free.
Conclusion	Our approach to total pancreatectomy virtually eliminates the warm ischemia time while allowing processing of the whole organ for islet isolation.
Keywords	Total pancreatectomy, autologous islet transplantation, chronic pancreatitis, warm ischemia.

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The authors whose names are listed immediately above certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

LIST OF SELECTED ABBREVIATIONS:
1) Chronic pancreatitis: CP
2) Autologous Islet Transplantation: AIT
3) Islet Equivalents: IE
4) Hemoglobin A1C: HbA1c
5) Chronic obstructive pulmonary disease: COPD
6) Miocardial infarct: MI
7) Deep vein thrombosis: DVT

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Case Description

Chronic pancreatitis (CP) causes progressive, irreversible and self sustained structural changes to the pancreas[1] ultimately leading to loss of both exocrine and endocrine function. Chronic, intractable pain and weight loss represent the cardinal symptoms of CP.

There are a variety of surgical options for pain relief, and the choice is based on the anatomical presentation of CP and the presence or absence of pancreatic duct dilation. Most surgeons would resect as little pancreatic tissue as possible in an attempt to preserve endocrine function. However, this has been shown to be elusive, as the natural history of chronic pancreatitis will invariably lead to a destruction of endocrine tissue in the vast majority of patients, regardless of the extent of initial surgery.[2]

Extensive and total pancreatectomy have been associated with the best outcomes in terms of pain relief[3] and when combined with autologous Islet Transplantation (AIT) may prevent onset of diabetes or provide at least a better glycemic control for those patients eventually requiring exogenous insulin.[4-8] The success rate of autologous islet transplantation largely depends on the remaining endocrine function, degree of pancreatic fibrosis determining the ability to digest the pancreas and to isolate the islets, and preservation of tissue viability during the pancreatectomy. To reduce ischemic damage, vascularization of the pancreas must be preserved until the very last moment, which in the context of pancreatectomy for advanced CP may represent a significant surgical challenge. Herein we present a safe technique to minimize warm ischemia time during pancreatectomy for CP.

A 57-year-old Caucasian man presented with a one-year history of severe alcohol-induced CP with disabling pain, 18 pounds weight loss, common bile duct stricture and recurrent pseudocysts on the pancreatic neck. The pain was not responsive to opiods medications and did not improve after two percutaneous drainage procedures of pancreatic pseudocyst localized at the neck of the organ, multiple endoscopic biliary stents. Past medical history was also significant for chronic obstructive pulmonary disease (COPD), myocardial infarction (MI), pulmonary hypertension and deep vein thrombosis (DVT).

In the presence of persistent bile duct obstruction, recurrent pseudocysts at the level the pancreatic neck and distal pancreas and rapidly deteriorating patient condition, the interdisciplinary team elected for total pancreatecomy with the attempt of AIT.

Antibiotic prohylaxis was administered prior to skin incision (cefazolin 1 gr. IV). The operation was started with a bilateral subcostal incision and separation of the gastrocolic ligament and short gastric vessels to expose the body and tail of the pancreas. After exposing the proper hepatic artery, common hepatic artery, and gastroduodenal artery, the duodenum and the head of the pancreas were mobilized and portal vein was exposed.

After cholecystectomy, the common bile duct was divided. At this time we explored visually and digitally the space between portal vein and the common bile duct to exclude the presence of an accessory or replaced right hepatic artery. The common hepatic artery was followed to the bifurcation of the splenic artery. We freed the superior pancreatic margin from the portal vein.

The duodenum was divided about 4 cm from the pylorus to allow preservation of the pylorus while preserving the vascular supply of the distal stomach.

At this point the tail was lifted up all the way to the bifurcation of the splenic and common hepatic artery and to the confluence of the splenic vein and the superior mesenteric vein. The spleen was removed in this case due to the presence of multiple abscesses involving the viscus and related to the previous history of splenic hemathoma under anticoagulation. In normal circumstances the routine splenectomy is not required with our technique. The left pancreas was dissected free leaving it attached only to the splenic vein and the splenic artery. The inferior mesenteric vein was preserved for islet infusion.

The superior mesenteric vein was dissected, exposed and an umbilical tape was passed behind the pancreatic neck. After placing two haemostatic sutures on the upper and lower pancreatic borders to the left and right of the umbilical tape, the pancreatic neck was transected. The pancreatic neck was detached from the superior mesenteric vein (SMV) and portal vein ("open book") (Figure 1).

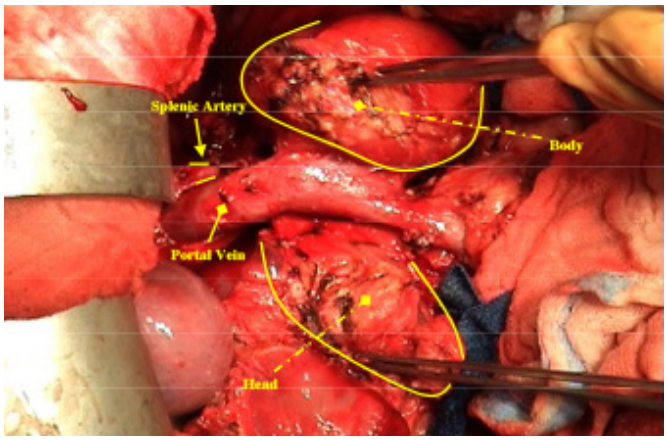

Figure 1. *"Open book maneuver".* Yellow arrows from top to bottom of the figure are pointing to *head of the pancreas, portal vein, splenic artery, body of the pancreas.*

Next, the splenic artery and splenic vein were clamped and divided and the body and tail of the pancreas were brought to the back table and immediately flushed with cold UW solution.

At this point the proximal jejunum was stapled and transected about 10 cm distally from the ligament of Treitz. Then the distal duodenum was brought to the right of the mesenteric artery and vein. The uncinate process was then freed from the surrounding tissue. The superior mesenteric artery (SMA) was identified at its take-off from the aorta and then followed down for about 3–4 cm. At this point, the pancreatic head was separated from the SMA and SMV with an endovascular stapler (Figure 2).

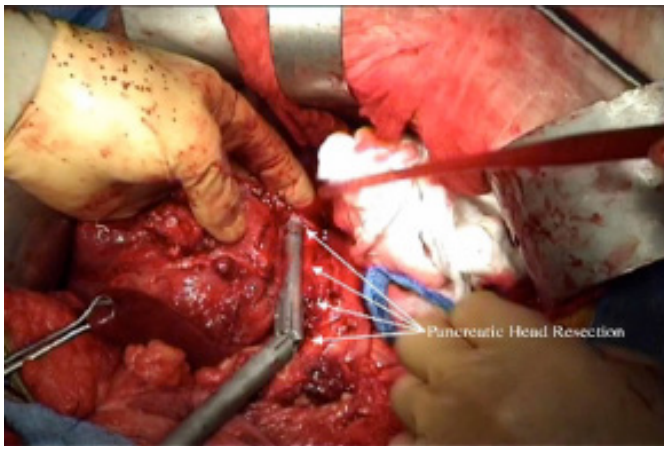

Figure 2. Pancreatic head harvest. White arrows are pointing to the Endo GIA™ staple line used to *transect the pancreatic head.*

On the back table the head of the pancreas and the duodenum were separated and the duodenum discarded. The pancreatic head and body-tail were then immediately washed with University of Wisconsin solution. The two portions of the pancreas were brought to the islet lab for islet isolation. The collagenase solution is then injected under pressure and intraductally in a separate fashio to the head and body-tail portions to digest the exocrine pancreas whilst sparing the islets. The digestion process takes place inside the "Ricordi chamber" at 37°C. The chamber is shaked to mechanically facilitate the freeing process of the islets. After digestion the islets tissue is suspended in culture medium and injected into the portal system as unpurified preparation. We do not purify the preparation because of the significant (up to 30 percent) loss of islets associated with the gradient separation method used for the purification process. In our case and with our technique a percentage of islet recovery from the body/tail vs. the head could not be established as the two portions of the organs are processed alltogether.

The reconstruction of the biliary and gastric continuity was performed as follows: a jejunal loop was brought to the liver hilum and an end-to-side hepaticojejunostomy was performed. After ensuring viability of the remaining duodenum an end-to-side duodenojejunostomy was performed in two layers using the omega jejunal loop.

An 18-french catheter was placed into the inferior mesenteric vein (IMV) and connected to a pressure monitor in preparation of the autologous islet infusion.

Five thousand units of heparin were given intra-portally as bolus before islet infusion under control of the portal pressure. Postoperatively, the patient was heparinized for 7 days aiming for a PTT of 40–50 sec.

The pancreas was exposed to less than 1 minute of warm ischemia time. The islet isolation procedure resulted in 40ml of unpurified tissue containing 250,000 Islet Equivalents (IE) (see sample in Figure 3).

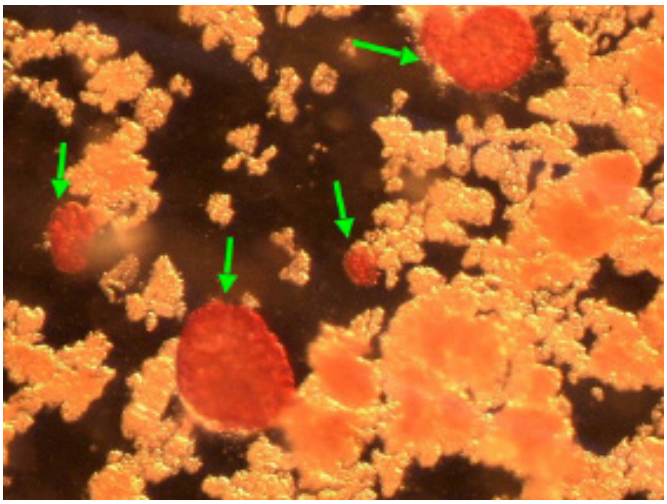

Figure 3. Dithizone staining/40X. Green arrows are pointing to the unpurified autologous Islets.

The islets were infused into the portal system via the 18-french catheter placed into the IMV. The starting portal pressure was 10 mmHg and raised to 19 mmHg at the end of the islet infusion. The operative time including islet isolation and infusion was 7.5 hours.

The patient had a surgically uncomplicated post-operative course. The postoperative recovery was delayed by complications related to congestive heart failure and exacerbation of COPD. The patient was discharged at post-operative day 28 when a regular diet was tolerated and the pain was controlled. Long-term morphine medication and insulin treatment were withdrawn before discharge.

At 1-year follow-up the patient was insulin-independent wit normal HbA1c and pain medication free.

Discussion

The exact pathophysiology of CP remains to be elucidated. The most comprehensive and most frequently recognized model for the development of CP is the so-called Sentinel Acute Pancreatitis Event (SAPE) model that is based on the hypothesis that a "sentinel event" (e.g., alcohol induced stress) triggers an initial inflammatory response that resolve completely or persists. In the latter case, the persistent inflammatory response leads to recruitment, activation and proliferation of pancreatic stellate cells and macrophages and if the process continues unimpeded, progressive fibrosis and parenchymal destruction[9]. These changes may cause severe, disabling pain and maldigestion that eventually culminate in narcotic addiction and malnutrition. Furthermore, 78.5 percent of patients with chronic pancreatitis are affected by type 3c diabetes mellitus (secondary to pancreatic diseases)[10] and are at increased risk for pancreatic adenocarcinoma in comparison to the general population. [11,12]

At least 50 percent of patients[13-15] who suffer from chronic pancreatitis will ultimately require some form of surgical intervention secondary to persistent refractory pain and/or complications of the disease.[16,17] Conservative surgery is associated with recurrence of symptoms or complications related to pancreatic disease in 30 to 50 percent of patients.[18-21] Total pancreatectomy may represent the most effective treatment for patients for whom both medical and standard surgical management has failed to provide relief. However the total pancreatectomy implies loss of both insulin-producing beta cells and glucagon-producing alpha cells. The lack of counter-regulatory mechanism mediated by the glucagon leads to onset of "brittle" surgical diabetes (higher frequency and severity of hypoglycemia) which may defeat the benefits of this radical approach. One study reported that post-surgical brittle diabetes was an important cause of death in 50 percent of the patients within five years after total pancreatectomy.[22]

This important limitation of total pancreatectomy can be mitigated by autologous transplantation of islets recovered from the surgically removed pancreas. In experimental models and human studies, long-term normal glycemia has been achieved following islet auto transplantation. [4-7]

Many factors affect the overall outcome of AIT. Concern has been expressed about the negative influence of the longer warm ischemia usually associated with total pancreatectomy. Despite significant technical advances in the last decade there is still a significant duration of warm ischemia in difficult cases. Warm ischemia is particularly detrimental to islet isolation because of the inapplicability of cold *in situ* vascular perfusion used with cadaver pancreas resection. Every technical effort directed to shorten the duration of warm ischemia may translate in higher islet viability and in overall better metabolic outcome. The transection of the pancreatic neck allows the dissection of both halves of the gland leaving them attached to the terminal branches of the splenic artery and vein for the body and tail and to the SMA and SMV for the head until the very last moment, virtually eliminating warm ischemia time. This maneuver allows the head to be used in the digestion step, optimizing the islet yield that is commonly compromised by the reduced islet mass related to CP.

Other authors suggested that in difficult cases the extra time needed to preserve the head is not worth taking and, after pancreas division across the portal vein, only body and tail should be sent for islet processing.[23]. This consideration must be weighted against the evidence that the head region of the pancreas contributes to approximately 30 percent of the total islet yield.[24]

Other centers have implemented a technique similar to ours as they initially mobilize and divide the distal portion of the pancreas along with the splenic artery and vein, at the level of the superior mesenteric vein and then send this portion to the islet isolation laboratory for the islet cell harvest while the remainder of the pancreas is being mobilized and resected.[25] This approach will imply two trips to the islet isolation laboratory and a separate and sequential processing of the two portions of the pancreas that inevitably prolongs the duration of the islet isolation step and therefore the overall skin-to-skin time of the surgical procedure.

In our "open book" technique the umbilical tape is passed behind the pancreatic neck then this is lifted up and transected whilst the vascular supply to both portions of the pancreas is kept intact until we are ready to divide in almost simultaneous fashion. The two portions of the pancreas are therefore being sent to the islet isolation laboratory and processed simultaneously.

An additional advantage and peculiarity of our technique is that the transection of the neck facilitates the dissection of the posterior plane of the gland on the mesenteric and portal axis and on the superior and inferior pancreatico-duodenal arcades and splenic vessels, which can be challenging because of severe fibrosis. The neck transection ensures a higher degree of mobility on both head and body of the pancreas during the dissection potentially limiting the blood loss. In our patient, using this technique, we reported a blood loss of 300 ml and no blood transfusion. In a previous study on 41 patients undergoing to total pancreatectomy with AIT[26] where full mobilization of the pancreas without separation of the neck was implemeted, a median blood loss of 2000ml was reported that required blood transfusion (mean 1,200ml/patient) in 95.1 percent of the patients. The authors of the most recent and largest series of total pancreatectomy with AIT (409 patients) who implemented the full mobilization technique (without the transection of the neck we routinely perform) quote in their paper that "In cases where head and duodenal mobilization was difficult, the body and tail were removed separately and sent to the islet processing lab before the proximal portion was removed".[27] The authors do not specify in how many cases they had to adopt this "sequential" technique but we do know that a considerable number of patients with chronic pancreatitis undergo a number of endoscopic procedures and are referred to the surgical team some times many years later after the intial diagnosis, one may assume that this number of patients had to be significant. This variation of the full mobilization technique may have contributed to the prolongation of the islet processing time that picked up to 6.5 hrs and averaged 4.5 hours after the pancreatectomy.
Some authors[28] criticized the neck transection arguing that it may increase the leakage of Collagenase solution from the free edge at the time of the enzymatic distension. In our experience the transection of the pancreatic capsule at the neck does not hamper the distension by the collagenase solution that is indeed limited by the grade of fibrosis. In limited cases we do modify our technique by the application of two circumferential sutures, along the free edge of the pancreatic section plan, to overcome this possible problem. We cannulate the main pancreatic duct at its exit from the head and on the free edge to the pancreatic body.

Advanced fibrosis associated with CP may profoundly alter the anatomical planes. In these circumstances the identification and dissection of the hepatic artery nearby the gastro duodenal artery or splenic artery may become a difficult task and consequently increase the risk of accidental transection. For this reason we prefer to identify and to dissect the hepatic artery at the hepatic hilum that represents a safer, consistent anatomical site and then we follow it down to the gastroduodenal artery and splenic artery at distance to the pancreas.

General consensus has been reached in literature about the benefits of preserving the pylorus. The pylorus preserving pancreatectomy is associated with a better outcome in terms of long-term, post-antrectomy symptoms, diabetes control and anastomotic ulceration.[29,30] Accordingly we attempt to resect, whenever possible, only the second portion of the duodenum along with the head of the pancreas to preserve the pylorus.

The preservation of the pylorus is also important because it may mitigate the need for high dose pancreatic enzyme supplementation to treat the complete exocrine insufficiency result of total pancreatectomy. The altered mixing and emptying resulting from the gastro-biliary-enteric reconstruction is indeed a significant contributor to these difficulties in treating the exocrine insufficiency. This spe-

cific sequela of total pancreatectomy followed by AIT is also a concern. Its clinical significance is somehow mitigated by the fact that many patients are already on pancreatic enzyme supplementation by the time they get referred to us.

We do believe that our technique could be potentially used and adopted by centers that do not have in-house islet isolation facility and expertise as long as the referral center is located within a reasonable distance from the accepting islet isolation lab/center. To note, a Clinical Islet Transplantation (CIT) Consortium has been created over recent years. This National Institutes of Health–sponsored organization includes eight manufacturing facilities across the US that have established "a harmonized process for the manufacture of allogeneic purified human pancreatic islet" and could potentially represent a reliable and efficient referral network for those centers that might have an interest to adopt our technique but do not have in-house islet isolation program/facilities.

Conclusion

Our approach to total pancreatectomy virtually eliminates the warm ischemia time while allowing processing of the whole organ for islet isolation.

Lessons Learned

Our case report indictated that the proposed surgical technique to minimize warm ischemia time during pancreatectomy for CP is safe and effective.

The favorable outcomes of our case suggest that AIT should be considered and possibly offered to patients undergoing total pancreatectomy for CP to prevent or minimize ischemic damage of the pancreatic islets to be isolated and transplanted in autologous manner.

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